THE

ORGANIC CHEMISTRY

OF NITROGEN

BY

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NEW EDITION

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PREFACE

THE first edition of this book was published in 1910, and in 1922 Professor Sidgwick began to make plans for bringing out a revised edition. His intention was to ask chemists in Oxford to help him by revising individual chapters and to write the final text himself, making use of the information compiled by these collaborators. During 1932–3 he completed the first draft of Chapters I, III, VIII, and XII. His many duties, however, prevented the fulfilment of this plan and in the summer of 1934 we were entrusted with the task of rewriting the whole book and took over all the material which had been accumulated. We have revised each chapter anew, and the text as it stands is ours with the exception of two sections mentioned later. Our labours have been considerably lightened by the preliminary work carried out by the original collaborators whose names are given below. We alone are responsible for the opinions expressed, which differ in some details from those of the collaborators.

The plan of the book remains essentially the same as in the first edition. The intention is to give an account of the simpler organic compounds of nitrogen and to discuss some of the interesting problems which their properties and behaviour present, giving as far as is possible adequate explanation of the necessary physical background. We have thought it best to keep the discussion as close as possible to the experimental data and not to embark on any lengthy theoretical treatment of the facts. The book is inevitably longer than in its first edition because of the greater number of known facts. Two subjects discussed in that edition have been omitted, the derivatives of purine and the simpler alkaloids. The chief reason for the first of these omissions is that neither of us felt that his own knowledge of purine chemistry was adequate for a proper treatment of the subject, and for the second that descriptions of the alkaloids are to be found in other works in English and that the space so gained could be profitably devoted to a fuller description of the fundamental chemical properties of the simpler heterocyclic compounds. One of our chief difficulties has been to decide how much space should be allotted to the various classes of compounds. Not unnaturally we have given somewhat greater attention to the subjects where, because of our own knowledge, we have felt on surer ground.

Among those who have collaborated in collecting material mention must first be made of Mr. K. F. Armstrong who was killed in a ski-ing accident in Austria in January 1935. For the last six months of his life he had been collecting data for Chapters V and X, and he had also written valuable notes on the material compiled by others for Chapters IV and XVII. His death at the early age of 25 deprived us of one of the most valuable of our collaborators.

The following gentlemen have assisted by collecting material and in

some cases by writing preliminary drafts for various chapters: Dr. J. C. Smith, Chapters XII and XV and the section on nitrophenols in Chapter VIII; Mr. D. Ll. Hammick, Chapters VII and VIII; Prof. J. M. Gulland, Chapter IV; Dr. S. G. P. Plant, Chapters XVII and XVIII; Dr. R. G. A. New, Chapter X, especially the section on isocyanides; Dr. E. Hope, Chapters XIII and XIV; Dr. F. E. King in preliminary work on Chapter V; Dr. F. M. Brewer, in preliminary work on Chapter I and in the beginning of the organization of the revised edition. Mr. Hammick has contributed the section on the molecular complexes of aromatic nitro compounds in Chapter VIII and Professor Sidgwick that on chelate o-nitrophenol derivatives in the same chapter; in the text their initials are appended to these articles.

Many of these gentlemen have helped by reading and criticizing various sections of the final text, and their comments have added greatly to its accuracy. Dr. A. Weissberger also gave great assistance in this way while he was in Oxford, particularly in Chapters IX, X, and XI. Professor R. Robinson was always willing to discuss difficult points and these discussions have been of great value especially for Chapters XII and XVII. Finally, Professor Sidgwick read almost the whole manuscript in its final form and wrote detailed critical notes on it; these have contributed largely towards clarity and accuracy in the text.

The references given are not intended to be complete. References to the early work can be found in Beilstein's *Handbuch* and Meyer and Jacobson's *Lehrbuch*. Those which appear are for the most part either to the more important papers or to the comparatively recent work which is not yet included in those two standard works. Our thanks are due to Mrs. T. W. J. Taylor who has spent much time in checking all the references with the original literature and in helping with proof-reading. The diagram on page 42 is taken from G. Wittig's *Stereochemie*, published by the Akademische Verlagsgesellschaft, Leipzig 1930.

<div style="text-align: right">T. W. J. T.</div>

November 1936   W. B.

NOTE

Under present circumstances it has not been possible to make the many additions and alterations which would be required to bring the book up to date. The opportunity has been taken to correct errors and to make some minor modifications of the text. Part of the section on Molecular Complexes formed by aromatic nitro compounds (p. 261) has been rewritten by Mr. D. Ll. Hammick, and a note has been added on *cis*-azobenzene (p. 456).

In making these alterations it has not been possible to consult with Mr. T. W. J. Taylor who is away on War Service, and responsibility for them is mine.

<div style="text-align: right">W. B.</div>

May 1942

CONTENTS

ABBREVIATIONS

A = Ångström unit, 10^{-8} cm.

A, see footnote, page 107.

Ac = an acyl radical, such as acetyl, $CH_3 \cdot CO$.

Ar, Ar′ = an aromatic monovalent radical, such as tolyl, $CH_3 \cdot C_6H_4$.

Bz = benzyl, $C_6H_5 \cdot CH_2$.

D = Debye unit of electric moment, 10^{-18} electrostatic units.

Et = ethyl, C_2H_5.

M = an atom of a monovalent metal.

Me = methyl, CH_3.

R, R′, &c. = a monovalent organic group, except where otherwise described; usually an alkyl group.

R, see footnote, page 106.

X = a monovalent group; often an anion such as Cl^-.

ϕ = phenyl, C_6H_5.

[ ] indicates an ion, either kation or anion, except when used to indicate a concentration term in an equilibrium constant.

ABBREVIATIONS FOR TITLES OF JOURNALS

Ahrens' Sammlung. F. B. Ahrens' Sammlung chemischer und chemisch-technischer Vorträge.

Amer. Chem. J. American Chemical Journal.

Annalen. J. Liebig's Annalen der Chemie.

Anal. soc. españ. fis. quim. Anales de la sociedad española de física y química.

Ann. Chim. Annales de Chimie.

Ann. Chim. Phys. Annales de Chimie et de Physique.

Ann. Physik. Annalen der Physik.

Ann. Reports C. S. Annual Reports of the Progress of Chemistry; the Chemical Society.

Ann. Rev. Biochem. Annual Review of Biochemistry.

Arch. exp. Path. und Pharm. Archiv für experimentelle Pathologie und Pharmakologie.

Arch. Pharm. Archiv der Pharmazie.

Arch. Sci. phys. nat. Archives des Sciences physiques et naturelles.

Arkiv f. Kemi. Arkiv för Kemi, Mineralogi och Geologi.

Atti R. Atti della Reale Accademia Nazionale dei Lincei.

Ber. Berichte der deutschen chemischen Gesellschaft.

Biochem. J. Biochemical Journal.

Biochem. Z. Biochemische Zeitschrift.

Bull. Acad. roy. Belg. Académie royale de Belgique—Bulletin de la Classe des Sciences.

Bull. Soc. chim. Bulletin de la Société chimique de France.

Bull. Soc. chim. Belg. Bulletin de la Société chimique de Belgique.

Bull. Soc. Chim. biol. Bulletin de la Société de Chimie biologique.

Bur. Standards J. Bureau of Standards Journal of Research.

C.r. Comptes rendus hebdomadaires des Séances de l'Académie des Sciences.

C.r. du Lab. Carlsberg. Comptes rendus des travaux du Laboratoire de Carlsberg.
Canad. J. Res. Canadian Journal of Research.
Chem. and Ind. Chemistry and Industry Review.
Chem. News. Chemical News.
Chem. Rev. Chemical Reviews.
D. R.-P. Deutsches Reichs-Patent.
Eng. Pat. English Patent.
Fried. P. Friedlaender's Fortschritte der Teerfarbenfabrikation.
Gazz. Gazzetta chimica italiana.
Helv. Chim. Acta. Helvetica Chimica Acta.
Ind. Eng. Chem. Industrial and Engineering Chemistry.
J. Amer. C. S. Journal of the American Chemical Society.
J. biol. Chem. Journal of biological Chemistry.
J. C. S. Journal of the Chemical Society.
J. Chem. Phys. Journal of Chemical Physics.
J. Gen. Chem. Russ. Journal of General Chemistry, Russia.
J. Gen. Physiol. Journal of General Physiology, Baltimore.
J. Ind. C. S. Journal of the Indian Chemical Society.
J. Phys. Chem. Journal of Physical Chemistry.
J. Physiol. Journal of Physiology.
J. pr. Chem. Journal für praktische Chemie.
J. Russ. Phys. Chem. Soc. Journal of the Physical and Chemical Society of Russia.
J.S.C.I. Journal of the Society of Chemical Industry.
J. Soc. Dyers and Colour. Journal of the Society of Dyers and Colourists.
Mem. Coll. Sci. Kyoto Imp. Univ. Memoirs of the College of Science, Kyoto Imperial University.
Mém. Poudres. Mémorial des Poudres.
Monats. Monatshefte für Chemie und verwandte Teile anderer Wissenschaften.
Naturwiss. Naturwissenschaften.
Österr. bot. Z. Österreichische botanische Zeitschrift.
Pharm. J. Pharmaceutical Journal.
Phil. Trans. Philosophical Transactions of the Royal Society of London.
Phys. Review. Physical Review.
Phys. Z. Physikalische Zeitschrift.
Pogg. Ann. J. C. Poggendorff's Annalen der Physik und Chemie.
Proc. K. Akad. Wetensch. Amsterdam. Koninklijke Akademie van Wetenschappen te Amsterdam. Proceedings.
Proc. Nat. Acad. Sci. Proceedings of the National Academy of Sciences.
Proc. Roy. Soc. Proceedings of the Royal Society.
Quart. J. Physiol. Quarterly Journal of Experimental Physiology.
Rec. trav. chim. Recueil des travaux chimiques des Pays-Bas.
Rev. chim. ind. Revue de chimie industrielle.
S. African J. of Science. South African Journal of Science.
Sitz. Akad. Wiss. Wien. Sitzungsberichte der Akademie der Wissenschaften, Wien.
Trans. Faraday Soc. Transactions of the Faraday Society.
Trans. Roy. Soc. Canada. Transactions of the Royal Society of Canada.
Trans. Roy. Soc. Edin. Transactions of the Royal Society of Edinburgh.
Z. angew. Chem. Zeitschrift für angewandte Chemie.

Z. anorg. Chem. Zeitschrift für anorganische und allgemeine Chemie.

Z. Biologie. Zeitschrift für Biologie.

Z. Elektrochem. Zeitschrift für Elektrochemie.

Z. f. Chem. Zeitschrift für Chemie.

Z. ges. Schiess- u. Sprengstoffw. Zeitschrift für das gesamte Schiess- und Sprengstoffwesen.

Z. Krist. Zeitschrift für Kristallographie.

Z. phys. Chem. Zeitschrift für physikalische Chemie.

Z. physiol. Chem. Hoppe-Seyler's Zeitschrift für physiologische Chemie.

Z. Wiss. Photograph. Zeitschrift für wissenschaftliche Photographie, Photophysik und Photochemie.

Zent. Chemisches Zentralblatt.

INTRODUCTION

By N. V. SIDGWICK

THE NITROGEN ATOM

NEXT to carbon, nitrogen is the most important element in organic chemistry for the variety and interest of the compounds into which it enters. Some remarks about the general characteristics of the element may conveniently precede the discussion of its organic compounds.

Nitrogen, atomic number 7, is the lightest element of the fifth periodic group, and so has 5 valency electrons. In nearly all its compounds it increases this number to 8. It cannot do this by direct addition, with the formation of a trivalent anion N^{---}, because this triple charge would cause so great a deformation of the orbits by the cation that the electrovalency would pass over into a covalency.[1] Hence it is by the sharing of electrons—by the formation of covalencies—that the necessary electrons are gained. In this way two normal states of the nitrogen atom can arise, (1) trivalent and tricovalent, as in NH$_3$, with a valency group of 8 electrons, 6 shared (I), and (2) 4-covalent with a fully shared octet, in which the nitrogen, since it uses all its 5 valency electrons, is pentavalent. The fourth covalency can be established by co-ordination of the lone pair of the trivalent atom acting as a donor, and the acceptor may either be a positive ion as H$^+$ (or a univalent radical as methyl, losing an electron on combination), in which case a positive ammonium ion is formed (II a), or the acceptor may be a neutral divalent atom such as oxygen, when the product is a neutral molecule (II b).
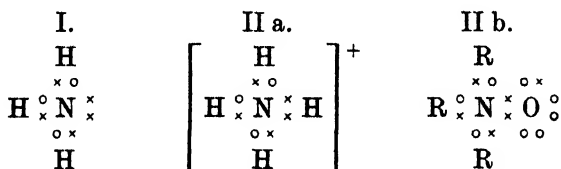
A 5-covalent state, like that of phosphorus in the pentafluoride PF$_5$, is impossible for nitrogen, because the elements in the first short period are limited in their covalency to 4, as was first pointed out by Werner (see p. 32).

In addition to these normal states, we find a certain number of compounds of nitrogen in which there is one electron more (or one less) in the molecule than is required for the completion of the octet, the resulting molecule having an odd number of electrons (the 'odd molecules' of G. N. Lewis). The most familiar of these are the two oxides nitric oxide NO and the monomeric form of nitrogen peroxide NO$_2$; a series of organic derivatives of these types have also been prepared (see p. 165 and 388).

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[1] It is possible that this ion may occur in some inorganic nitrides.

These molecules are found to be paramagnetic, as we should expect (all ordinary organic substances are diamagnetic), and the nitrogen always tends to revert to a normal state of combination. The state of linkage in such molecules as these cannot be expressed in the ordinary symbols, and the occurrence of these unusual forms of attachment can in fact only be understood in the light of the theory of resonance discussed in the next section (p. xv).

The heats of formation of the links of nitrogen to other atoms are of importance as determining the thermodynamic stability of its compounds. Their values are in many cases approximately known, and do not vary greatly (apart from the occurrence of resonance) with changes in the other parts of the molecule. The values required are those of the formation of the link in the gaseous state from the component atoms, and hence involve a knowledge of the heats of atomization of the elements concerned. In the list below that of carbon is assumed to be 169 and that of nitrogen 84·5 kcals.[1]

Heats of Formation of Links from Atoms

(Kcals. per gm. mol. in the gas at 25°.)

N—H 83　　　　N—F 69　　　　N—Cl 39　　　　N—O 49 ?

	Abs.	Rel.		Abs.	Rel.		Abs.	Rel.	Mean
N—N	23	1	C—C	80·5	1	C—N	59	1	51·8
N=N	61	2·7	C=C	142	1·7	C=N	121·5	2·1	101·5
N≡N	169	7·4	C≡C	189·5	2·4	C≡N	180	3·1	179·3

The most important conclusion which emerges from these figures is the very different effects of multiplicity on the heat of formation in carbon and in nitrogen. As will be seen, the heat value rises less rapidly than the multiplicity with C—C, and much more rapidly with N—N; with the links of carbon to nitrogen the rise is almost exactly proportional to the number of links; in fact the value is in every case very nearly the mean of those for C—C and N—N, as the last column in the table shows. This corresponds to a fundamental difference in behaviour between carbon and nitrogen. In a carbon chain the presence of a multiple link is, as is well known, a sign of weakness: the chain is likely to break between these two atoms. A double link between two nitrogen atoms, on the contrary, is a sign of strength: the chain never breaks at that point, except on reduction with hydrogen, for which, as the heat values show, nitrogen has a peculiarly strong affinity; the tendency is for the double nitrogen link to turn into a triple link, i.e. for the —N=N— group to separate as nitrogen gas. This is what happens with the diazo compounds (both aromatic (p. 404) and aliphatic (p. 352)), and the azides (p. 368) and the azo-compounds (p. 432).

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[1] These must replace the incorrect values of 150 for carbon and 104 for nitrogen previously assumed, e.g. in my *Covalent Link*, 1933; see for nitrogen R. S. Mulliken, *Phys. Rev.* 1934, ii, **46**, 144; G. Herzberg and H. Sponer, *Z. phys. Chem.* 1934, B, **26**, 1; for carbon E. C. Baughan, *Nature*, 1941, **147**, 542; G. J. Kynch and W. G. Penney, *Proc. Roy. Soc.* 1941, **179**, 214.

Even a singly linked pair of nitrogen atoms often breaks off in the form of elementary nitrogen, as with phenylhydrazine on treatment with copper sulphate (p. 382).

Since the heat of formation of the link between carbon and nitrogen is so closely proportional to the multiplicity, we should expect the stability of the single, double, and treble links to be much the same. The observed facts do not quite agree with this. The triple C≡N link is not much less stable than the single, but in certain reactions, especially hydrolysis, the double link C=N, as in the imines, the Schiff bases, and the anils (p. 65), is much less stable than either.[1]

RESONANCE

[This subject is the main theme of L. Pauling's *The Nature of the Chemical Bond* (Cornell University Press, 1939). Among the most important papers are Pauling, *J. Amer. C. S.* 1932, **54**, 988, 3570 (covalent and electrovalent links): idem, *Proc. Nat. Acad. Sci.* 1932, **18**, 293, 498 (interatomic distances): Pauling and D. M. Yost, ibid. 414: Pauling and J. Sherman, *J. Chem. Phys.* 1933, **1**, 606 (heats of formation): Pauling and G. W. Wheland, ibid. 362: Pauling and J. Sherman, ibid. 679 (application to aromatic and hydroaromatic compounds): G. W. Wheland, ibid. 731 (keto-enols): L. O. Brockway and L. Pauling, *Proc. Nat. Acad. Sci.* 1933, **19**, 860 (organic azides): L. E. Sutton, *Trans. Faraday Soc.* 1934, **30**, 801 (dipole moments and resonance). See further C. K. Ingold, *Chem. Rev.* 1934, **15**, 225 (resonance and organic reactivity).]

The conception of resonance is the most important development which structural chemistry has had since it was extended to three dimensions by van 't Hoff in 1874. It is a result of the application of wave-mechanics, and could not have been deduced from classical dynamics; but its essential conclusions can be stated very simply. If a molecule can have two or more different structures in the ordinary organic sense of the term, then under certain conditions its actual state is neither one nor the other, but something intermediate between the two, which partakes to some extent of the properties of both, but cannot be expressed in the usual structural symbols. The molecule is then said to exhibit resonance, and to be a resonance-hybrid of the two or more structures.

The conditions for resonance to be possible between two structures are these: I. The relative positions of the atoms in space must be nearly the same in both. II. The two must not differ too greatly in stability, or, in other words, both formulae must be reasonably probable. III. The number of paired electrons must be the same in both; this last condition is practically always fulfilled, so long as we are not dealing with 'odd molecules'. The results of the resonance are the following: 1. The molecule has to some extent the properties of each constituent structure, though not

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[1] The value given above for the C=N link is obtained from the heat of combustion of the isocyanates R—N=C=O, using the value (181 kcals.) for the C=O link derived from carbon dioxide; this would seem to make a reasonable allowance for resonance.

necessarily to the same extent, the more stable form predominating.
2. The hybrid has a smaller energy content (a greater stability and heat of formation, a smaller heat of combustion) than either of the two structures.
3. The distances between the atoms are rather smaller than the normal. Of these effects the last is of small importance from the point of view of the reactivity and similar properties, but is very useful in detecting the occurrence of the phenomenon. The second is the most important of all, because it implies that resonance must always occur whenever it is possible, and also that its occurrence must always increase the stability of the molecule.

Resonance must be clearly distinguished from tautomerism. Both imply that we find only one compound when we expect on the structural theory to have two, but the resonance hybrid differs in that (1) it is one substance and not a mixture of two, (2) it can only occur when the two structures involve nearly the same positions of the atoms in space (so that it is impossible, for example, with the structures HCN and HNC), and (3) it must always be more stable than either of the two forms.

As an example where the resonance has been established by experimental tests of two kinds we may take carbon dioxide. This has three possible structures, the last two being identical. If we may assume that the length and the heat of formation of a co-ordinate link are the same as those of a normal covalency, the heats of formation of the three forms are nearly the same, since the values for C—O links are nearly proportional to the multiplicity. They are also all linear molecules, and the distances vary only to the small extent required by the change in multiplicity. Thus the essential conditions of resonance are satisfied, and we should expect it to occur. If it does so, the heat of formation of carbon dioxide should be greater, and the lengths of the links less, than corresponds to the structure $O=C=O$. That this is so is shown by the values in the following table; the observed C—O distance is 1·15 A instead of the normal $C=O$ length of 1·28 A [1] and the heat of formation is 32 kcals. greater than that calculated from the value for a carbonyl group in aldehydes and ketones [2]

	$O=C=O$	$O{\leftarrow}C{\leqq}O$	$O{\rightleftharpoons}C{\rightarrow}O$	Obs.
Distance, A. {	1·28 1·28 2·56	1·43 1·13 2·56	1·13 1·43 2·56	2·30
Heat of Formation from atoms, kcals. }	367	ca 370	ca 370	399

Familiar examples of resonance are afforded by the symmetry of the $-N{\displaystyle{\nwarrow^O_O}}$ group (indicated by the dipole moments), of the $-C{\displaystyle{\nwarrow^O_{O^-}}}$ ion, and of the NO_3^- and $CO_3^=$ ions. The crystallographic evidence shows that the

[1] L. Pauling, *Proc. Nat. Acad. Sci.* 1932, **18**, 293.
[2] L. Pauling and D. M. Yost ibid. 414; L. Pauling and J. Sherman, *J. Chem. Phys.* 1933, **1**, 606.

last two are plane structures, as is required by the tetrahedral theory for the formulae

$$O=N\begin{smallmatrix}\nearrow O \\ \searrow \bar{O}\end{smallmatrix} \qquad O=C\begin{smallmatrix}\nearrow \bar{O} \\ \searrow \bar{O}\end{smallmatrix}$$
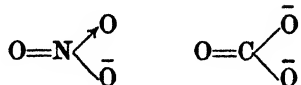
but further, that the three oxygen atoms are at the points of an equilateral triangle, with the nitrogen or the carbon at the centre. This implies a resonance, with the double link not localized on any particular oxygen atom. Here too we find the characteristic shortening of the link.[1]

The applications of the theory are numerous and important. It provides the physical support for the theories of organic reactivity developed by Lapworth, Robinson, Ingold, and others, and it elucidates the properties of many important groups of compounds, such as the simple free radicals (p. 390), the triphenylmethane dyes (p. 82), and the cyanine dyes (p. 561); it is of especial value in interpreting the behaviour of aromatic systems (pp. 488, 496). But there is one phenomenon of special interest which is explained by resonance and, as far as we can see, by resonance alone. This is the so-called co-ordinated or dicovalent hydrogen. For some years it has been recognized that under certain conditions a hydrogen atom is able to link two other atoms together, as in the association of hydroxylic compounds and the formation of the F_2H anion.

$$\begin{smallmatrix}R\searrow \\ H\nearrow\end{smallmatrix}O\cdots H-O-R \qquad [F-H\cdots F]$$
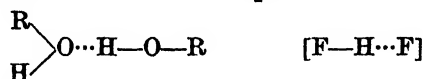
It was originally assumed that the hydrogen acted as the acceptor in a co-ordinate link $A:H:B$, having four shared electrons. Subsequent developments, while they have made it increasingly certain that hydrogen can act as a linking atom[2] have shown that this mechanism is impossible. It would be necessary for two of the four shared electrons to be in the second quantum group, and they would not be held firmly enough to account for the stability of the link. We therefore have to find some other mechanism for the link, and this is provided by the theory of resonance.

We can distinguish two sets of conditions under which this link occurs; firstly when it leads to the formation of a ring (chelate compounds), and secondly where the product is an open chain (association of hydroxylic compounds). Examples of chelate compounds are the β-keto-enols and the o-aldehydo-phenols. Here we have the two resonance structures, in
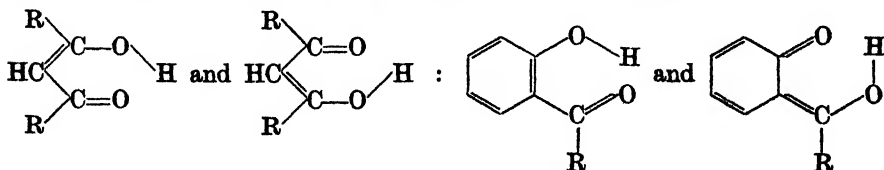

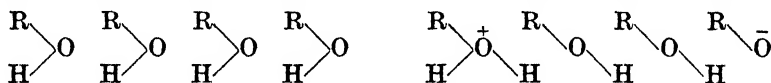[1] See V. M. Goldschmidt, Freudenberg's *Stereochemie*, 1933, p. 50.

[2] It has even been found possible to determine the length of the link, that is the distance between the nuclei of the oxygen or fluorine atoms in $O-H\cdots O$ and $F-H\cdots F$, which is about 2·5 A: see W. H. Zachariasen, *J. Chem. Phys.* 1933, 1, 634; J. West, *Z. Krist.* 1930, 74, 306.

one of which the hydrogen is attached to one of the oxygens, and in the other to the other. The strain in a 6-ring with two double links is very small, so that the same position of the atoms fits either structure. This mechanism explains the fact that two isomeric enols of this type have never been isolated. We can also see why the tendency to chelation practically disappears when the β-keto-enols are reduced to β-keto-alcohols, $R \cdot CH(OH) \cdot CH_2 \cdot CO \cdot R$, since the migration of the double link is no longer possible. In the o-phenol derivatives, such as the aldehydes and nitro-phenols (p. 268) we have to assume that the aromatic ring in the second structure is o-quinonoid: interesting evidence on this point has been given by W. Baker.[1]

Sometimes this ring-formation occurs by the combination of two molecules, as with the carboxylic acids.[2] These compounds can be shown to polymerize readily to double molecules but no further.

$$R \cdot C \underset{O-H \quad O}{\overset{O \quad H-O}{<>}} C \cdot R \qquad R \cdot C \underset{O \quad H-O}{\overset{O-H \quad O}{<>}} C \cdot R$$
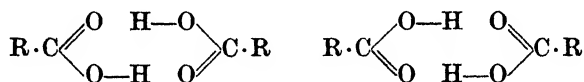
The association of the simpler hydroxylic compounds—water, alcohols, phenols—giving chains and not rings must be explained in some other way. Molecules of this kind are known to associate less readily in dilute solution than carboxylic acids or oximes, but with increasing concentration the polymerization increases indefinitely, and can go far beyond the dimeric stage.[3] This must occur through the formation of oxonium ions:

$$\underset{H}{\overset{R}{>}}O \quad \underset{H}{\overset{R}{>}}O \quad \underset{H}{\overset{R}{>}}O \quad \underset{H}{\overset{R}{>}}O \qquad \underset{H}{\overset{R}{>}}\overset{+}{O}\underset{H}{\overset{R}{<}}O \underset{H}{\overset{R}{<}}O \underset{H}{\overset{R}{<}}\overset{-}{O}$$

The length of the chain can be extended indefinitely, and it will in fact be determined by the balance between the resonance energy and the thermal agitation. It must be realized that the resonance depends on the atoms retaining their positions. Accordingly the RH_2O^+ and RO^- ions are not free to move so long as the resonance persists; the whole chain forms a 'zwitterion' and cannot contribute to the conductivity, which will be due only to those ions which are displaced from the chain by thermal agitation.

Co-ordination of Hydrogen attached to Nitrogen

The most familiar and important case of 'co-ordinated' hydrogen is that in which it links two oxygen atoms. The power of a hydrogen to link two other atoms in this way is wholly dependent on the nature of these atoms: it is almost nothing in C—H, small in N—H, larger in O—H, and still larger in F—H. When we pass from the first period to the second, it almost vanishes, being practically zero in P—H and S—H, and very small in Cl—H.

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[1] *J.C.S.* 1934, 1684; Baker and O. M. Lothian, ibid. 1935, 628; 1936, 274; W. Baker, *Nature*, 1936, **137**, 236.   [2] See *Ann. Reports C. S.* 1933, **30**, 115.

[3] See for example F. S. Brown and C. R. Bury, *J. Phys. Chem.* 1926, **30**, 694.

The tendency of hydrogen attached to nitrogen to form a further link is small, and is almost confined to one kind of grouping, which is, however, of considerable importance. This is the formation of an undissociated hydroxide from an amine and water. It has been shown (see p. 31) that the base, whether this is ammonia or a primary, secondary, or tertiary alkylamine, is present in aqueous solution to a considerable extent as the undissociated hydroxide, which may be written R_3N—H$\cdots$O—H. That the hydroxyl is attached through the amine hydrogen is shown by the fact that a quaternary hydroxide cannot form such a link and is accordingly a strong electrolyte. The linkage must be due to resonance between two forms, in one of which the linking hydrogen is attached to the nitrogen, and in the other to the oxygen of the hydroxyl; this gives us the very simple picture

$$R_3N—H \quad [OH] \qquad R_3N \quad H—OH.$$

It must be remembered that here, as in the associated alcohols described above, the R_3N and H—OH molecules are not free to move so long as the resonance with its accompanying gain of energy is maintained, and hence the amine molecules which are bound in this way to the water will not be soluble in a hydrocarbon solvent; they will thus appear, in the partition measurements of Moore and Winmill (p. 30), as a separate molecular species from the free R_3N.

Under any other conditions than these the power of the N—H hydrogen of forming a further link is very small. Ammonia itself is undoubtedly associated, as is proved by the absorption in the infra-red, but only to a very small extent. This must involve the structures

$$H_3N \quad H—NH_2 \qquad H_3\overset{+}{N}—H \quad \overset{-}{N}H_2.$$

Now the H_4N^+ ion is at least as stable as H_3O^+, and so the fact that ammonia is far less associated than water must be due to the anion $\overset{-}{N}H_2$ being much less stable than $\overset{-}{O}H$.

The linkage of nitrogen to oxygen through hydrogen can no doubt occur to some extent even when the ionic charges are not as favourable as in the ammonium hydroxides. This presumably explains the association of amides.
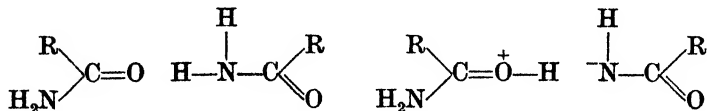
ESTERS OF HYPONITROUS, NITROUS, AND NITRIC ACIDS

ESTERS OF HYPONITROUS ACID, $R \cdot O \cdot N{:}N \cdot O \cdot R$

THE esters of hyponitrous acid have been prepared by the action of alkyl iodides on pure silver hyponitrite,[1] but have been little investigated. The simpler esters are colourless liquids, insoluble in water, which cannot be distilled without decomposition, even under reduced pressure. The benzyl ester is a solid melting at 48–49° which can be crystallized from a mixture of ether and light petroleum. The esters all show a normal molecular weight in benzene solution. They are unstable and decompose on standing at room temperature; the decomposition is faster at higher temperatures and on rapid heating they detonate with a somewhat violent explosion. In presence of water the hyponitrous esters are rapidly decomposed at temperatures above 40°, nitrogen being evolved:

$$\begin{matrix} EtO \cdot N \\ \parallel \\ N \cdot OEt \end{matrix} \longrightarrow EtOH + CH_3 \cdot CHO + N_2.$$

The constitution of these esters is shown by the fact that on reduction no amine can be detected; hence the alkyl groups cannot be attached to nitrogen. Since the molecule contains doubly linked nitrogen atoms, two geometrically isomeric forms of an ester might exist, just as geometrical isomerism is found in the diazohydrates and diazocyanides (see p. 417); these would correspond to *cis* and *trans* arrangements of the alkoxy groups about the two nitrogen atoms. No such isomerism has, however, been observed. The electric moment of the ethyl ester is 1·5 D and that of the benzyl ester 0·4 D.[2] These comparatively small values suggest that the esters exist in the *trans* configuration which is shown in the equation above. In spite of the fact that this formula, as written, implies that the molecule has a centre of symmetry, it is not to be expected that it would have zero moment, because of the free rotation about the oxygen valencies which do not lie in one straight line. The case is similar to that of the dimethyl ether of quinol
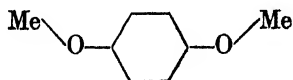
which has a moment of 1·74 D. In this compound the methyl groups do not lie on the line joining the centre of the ring to the oxygen atoms and

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[1] W. Zorn, *Ber.* 1878, **11**, 1630; A. Hantzsch and L. Kaufmann, *Annalen*, 1896, **292**, 329; J. R. Partington and C. C. Shah, *J.C.S.* 1932, 2593.

[2] E. C. E. Hunter and J. R. Partington, ibid. 1933, 309.

can occupy a series of positions by rotation about the valencies which unite the oxygen atoms to the ring.

ESTERS OF NITROUS ACID, $R \cdot O \cdot N{:}O$

The esters of nitrous acid can be prepared very easily by the action of nitrous fumes (containing nitrogen peroxide, nitrogen trioxide, and nitric oxide) on the alcohols, or by treating a mixture of an alcohol and solid or aqueous sodium nitrite with sulphuric acid. A similar reaction takes place when the vapour of nitrosyl chloride, NOCl, is passed into an alcohol in presence of an equivalent of pyridine.[1] The reactions can be regarded as those of the acid anhydride, the free acid, and the acid chloride, respectively. The rapid esterification of alcohols by nitrous acid in dilute aqueous solution is especially noteworthy. The esters of nitrous acid are also formed by the action of alkyl halides on silver nitrite, a certain amount of the isomeric nitroparaffin, $R \cdot NO_2$, being obtained at the same time; the proportion in which the two isomers are formed is discussed later (p. 229).

The nitrous esters of the lower alcohols are gases or volatile pleasant-smelling liquids which boil at considerably lower temperatures than the corresponding alcohols or the isomeric nitroparaffins (see Table, p. 7). Many of the liquid esters decompose slowly if kept at room temperature and evolve nitrous fumes. In the gas phase the alkyl nitrites decompose rapidly at about 200°, giving nitric oxide, the alcohol, and the aldehyde, as in the equation

$$2CH_3 \cdot CH_2 \cdot ONO \longrightarrow 2NO + CH_3 \cdot CH_2OH + CH_3 \cdot CHO.$$
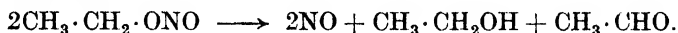
The reaction is homogeneous and unimolecular. The first stage has been shown to be the dissociation of the nitrite into nitric oxide and a free radical.

$$EtONO \longrightarrow NO + EtO{-}$$
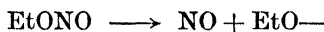
The latter undergoes further rapid reactions which lead to the alcohol and aldehyde.[2] When the alkyl nitrites are reduced by reagents such as tin and hydrochloric acid they are hydrolysed and yield the corresponding alcohols together with either hydroxylamine or ammonia. This shows that the nitrogen atom is not attached directly to carbon, but through oxygen, and stands in contrast to the reduction of the isomeric nitroparaffins which yields compounds such as amines, in which the alkyl group is attached to nitrogen. Catalytic reduction of the nitrites by hydrogen in presence of finely divided nickel or copper at temperatures above 100° causes isomeric change within the molecule and gives the reduction products of the nitroparaffins. This is to be expected, as the nitro compounds can be formed by passing the vapour of the nitrites through a hot tube packed with glass

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[1] L. Bouveault and A. Wahl, *C.r.* 1903, **136**, 1563; for the equilibrium in the gaseous system, MeOH + NOCl $\rightleftharpoons$ MeONO + HCl, see J. A. Leermakers and H. C. Ramsperger, *J. Amer. C. S.* 1932, **54**, 1837.

[2] E. W. R. Steacie and G. T. Shaw, *Proc. Roy. Soc.* 1934, **146**A, 388; *J. Chem. Phys.* 1935, **3**, 344; F. O. Rice and E. L. Radowskas, *J. Amer. C. S.* 1935, **57**, 350.

wool. With the methyl and ethyl derivatives the change occurs at 100–130°, increased temperature causing decomposition.[1] At 130° reduction gives the primary amines,[2] at higher temperatures secondary amines are formed,[3] while above 300° the nitrile is produced.[4]

The action of excess of zinc- or magnesium-alkyl halide on the nitrous esters yields an addition product which can be hydrolysed to an N-di-substituted hydroxylamine.[5] The first product is almost certainly a nitroso compound which reacts with the excess of organo-metallic compound in the normal way to give the hydroxylamine:[6]

$$RO \cdot NO + R'MgBr \longrightarrow ROMgBr + R' \cdot NO$$
$$R' \cdot NO + R'MgBr \longrightarrow R_2'NOMgBr \longrightarrow R_2'NOH.$$
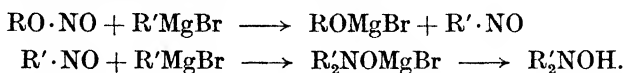
Among esters in general those of nitrous acid occupy a unique position in the ease with which they are both formed and decomposed. The formation of an ester from an alcohol and an acid is in the majority of cases a comparatively slow reaction which even in the presence of catalysts may take several hours. If, however, an aqueous solution of sodium nitrite and benzyl or amyl alcohol is acidified with a little hydrochloric acid, it instantly becomes milky owing to the separation of the nitrous ester. These esters are also very rapidly hydrolysed to the alcohol and nitrous acid by aqueous mineral acids. The rates of the formation and of the hydrolysis of ethyl and amyl nitrites have been measured by W. M. Fischer[7] who found that ethyl nitrite is hydrolysed to some extent by water alone; at a concentration of $N/43$ the equilibrium mixture contains 16 per cent. of the ester. In presence of hydrochloric acid, even at low concentrations, the hydrolysis is practically complete in a few minutes and the reaction velocity is much higher than with esters of other acids. On the other hand, the velocity constant for the hydrolysis of ethyl nitrite by aqueous sodium hydroxide is of the same order of magnitude as that for the hydrolysis of the esters of carboxylic and sulphonic acids. In this respect the esters of nitrous acid resemble the acetals, $RCH(OR')_2$, which are stable in alkaline solution, but rapidly hydrolysed by traces of mineral acids.

The ease with which the alkyl nitrites decompose into an alcohol and nitrous acid makes it possible to use them as a convenient source of nitrous acid in reactions where the usual method of obtaining that acid, from sodium nitrite, cannot be applied. Thus aromatic diazonium salts cannot be obtained in the solid state from their aqueous solutions because they are very soluble in water and decompose during the concentration of their solutions; they can, however, be prepared in alcoholic solution with an

[1] P. Neogi and T. Chowdhuri, *J.C.S.* 1916, **109**, 701.
[2] P. Neogi and T. Chowdhuri, ibid. 1917, **111**, 899.
[3] G. Gaudion, *Ann. Chim. Phys.* 1912, **25**, 125.
[4] A. Mailhe and M. L. Bellegarde, *Bull. Soc. chim.* 1919, **25**, 588.
[5] J. Bewad, *Ber.* 1907, **40**, 3065.
[6] H. Gilman and J. Robinson, *Rec. trav. chim.* 1929, **48**, 328.
[7] *Z. phys. Chem.* 1908, **65**, 61.

alkyl nitrite in place of nitrous acid and caused to separate in the crystalline condition by the addition of ether (see p. 401). The alkyl nitrites also appear to act merely as a source of nitrous acid in their condensations with compounds which contain a reactive methyl or methylene group. The reaction takes place in presence of sodium or potassium ethoxide or of hydrogen chloride and is discussed later (p. 171): it leads to the formation of an oximino compound; thus ethyl nitrite with phenylacetic ester and potassium ethoxide in alcoholic solution gives the potassium salt of the oxime of phenylglyoxylic ester:[1]

$$EtO \cdot NO + \phi CH_2 \cdot CO_2Et + KOEt \longrightarrow 2EtOH + \phi \cdot \underset{\underset{NOK}{\|}}{C} \cdot CO_2Et.$$
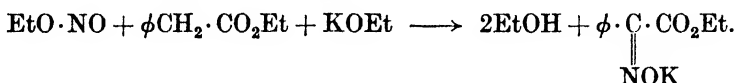
The action of an alkyl nitrite on a reactive phenol is similar; a nitrosophenol is formed just as though the phenol had been treated with nitrous acid. In these reactions the so-called amyl nitrite is often used because it is less volatile than the lower alkyl nitrites and consequently is easier to handle; it is made from the amyl alcohol of fusel oil and is mainly isoamyl nitrite. This compound has also found some use in medicine, since inhaling the vapour accelerates the action of the heart; for this reason care must be exercised when the compound is used.

The ease of formation and decomposition of the esters of nitrous acid obviously demands some explanation. Some of the suggestions that have been put forward are inadequate to explain all the facts. Thus it has been pointed out that nitrous acid exists in aqueous solution partly as the acid anhydride N_2O_3, which can be extracted from concentrated solutions of the acid by organic solvents, and it has been suggested that the rapid formation of the esters is due to the interaction of this anhydride with the alcohol. Other acids, however, are known, notably carbonic acid and sulphurous acid, which also exist partly as their anhydrides in aqueous solution, but the esters of these acids cannot be obtained with the same ease as the nitrous esters. Others have suggested that the esterification of nitrous acid and the hydrolysis of its esters are so rapid that the reactions should be regarded as involving ions and not molecules. There is little evidence to support such a view: the reaction velocities, although high, are measurable, while those of ionic reactions are not. Further, the formation of the ester can only be written as an ionic reaction if the nitrous acid is assumed to dissociate into the ions HO^- and NO^+, and there is no evidence of any such dissociation.

An entirely different hypothesis was put forward by A. von Baeyer and V. Villiger,[2] and in a modified form it provides the most satisfactory explanation for the exceptional behaviour of nitrous acid and its derivatives, although direct experimental evidence in its support is lacking. The essence of this hypothesis is that nitrous acid and its esters contain a trivalent nitrogen atom and thus, in virtue of the unshared pair of

[1] W. Wislicenus and R. Grützner, *Ber.* 1909, **42**, 1930.   [2] *Ber.* 1901, **34**, 755.

electrons of that atom, may form addition complexes with water, alcohols, and mineral acids, while there is no such possibility for a carboxylic acid or ester in which the carbon atom of the carboxyl group has all its electrons shared. The formulae for the addition complexes which were originally proposed by Baeyer and Villiger contain a penta-covalent nitrogen atom, a state of combination which, for reasons given elsewhere in this book (p. 32), is very unlikely, but they can easily be modified to overcome this difficulty. The modified scheme is as follows: nitrous acid in water is assumed to be in equilibrium with a hydrated form,

$$O:NOH + H_2O \rightleftharpoons O \leftarrow N \overset{\displaystyle OH}{\underset{\displaystyle H}{-OH}},$$
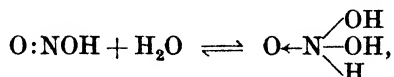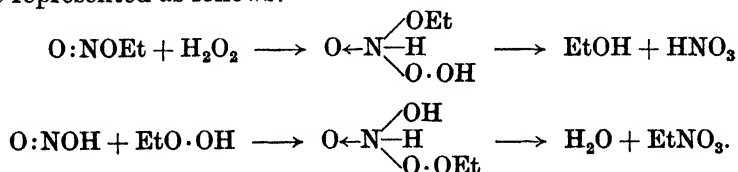
which in constitution resembles phosphorous acid: nitrous acid and an alcohol may form a similar compound which by simple loss of water can give the nitrous ester:

$$O:NOH + ROH \rightleftharpoons O \leftarrow N \overset{\displaystyle OR}{\underset{\displaystyle H}{-OH}} \rightleftharpoons O:NOR + H_2O.$$
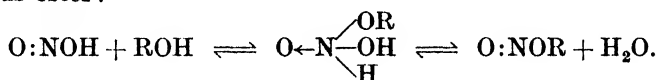
If the rate of formation of the addition complexes is high, the rapid esterification is accounted for, and also the rapid hydrolysis of the ester, since with excess of water the equilibria shown will be displaced from right to left. The exceptionally rapid hydrolysis by mineral acids can be formulated on the same basis:

$$O:NOR + HCl \rightleftharpoons O \leftarrow N \overset{\displaystyle OR}{\underset{\displaystyle Cl}{-H}} \rightleftharpoons ROH + NOCl,$$
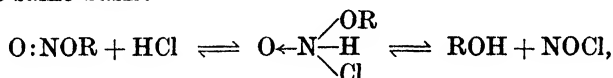
the nitrosyl chloride being removed from the equilibrium by interaction with the water. Baeyer and Villiger further showed that the somewhat unexpected action of hydrogen peroxide and its alkyl derivatives can be interpreted on the same scheme. They found that ethyl nitrite and hydrogen peroxide give at once ethyl alcohol and nitric acid, while nitrous acid and ethyl hydroperoxide give ethyl nitrate and water. These reactions can be represented as follows:

$$O:NOEt + H_2O_2 \longrightarrow O \leftarrow N \overset{\displaystyle OEt}{\underset{\displaystyle O \cdot OH}{-H}} \longrightarrow EtOH + HNO_3$$

$$O:NOH + EtO \cdot OH \longrightarrow O \leftarrow N \overset{\displaystyle OH}{\underset{\displaystyle O \cdot OEt}{-H}} \longrightarrow H_2O + EtNO_3.$$

Similarly ethyl nitrite and ethyl hydroperoxide give ethyl nitrate and ethyl alcohol:

$$O:NOEt + EtO \cdot OH \longrightarrow O \leftarrow N \overset{\displaystyle OEt}{\underset{\displaystyle O \cdot OEt}{-H}} \longrightarrow EtOH + EtNO_3.$$
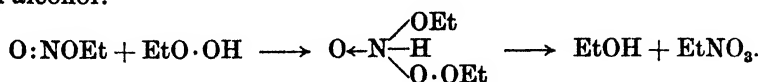
Further support for this view is to be found in the very great ease with which the alkyl group of a nitrous ester is exchanged for that of an alcohol

in which it is dissolved. This reaction (*Umesterung*) is common to all esters, but takes place with exceptional rapidity with the nitrites; if ethyl nitrite is dissolved in methyl alcohol, gaseous methyl nitrite begins to be evolved at once. The ready exchange may be due to the same complex formation postulated in the above cases:

$$O:NOEt + MeOH \rightleftharpoons O{\leftarrow}N\!\!\begin{array}{c}{\diagup}OEt\\{-}OMe\\{\diagdown}H\end{array} \rightleftharpoons O:NOMe + EtOH.$$
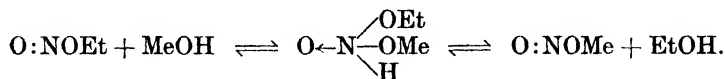
Finally it may be mentioned that nitric acid and its esters do not show the exceptional behaviour of the nitrous derivatives, but resemble the carboxylic compounds. This fact is in accord with the hypothesis, since in nitric acid and its esters the nitrogen atom has all its electrons shared. The hypothesis of addition complexes is obviously attractive and gives a consistent explanation for a large number of experimental facts. Whether it is actually true, it is difficult to say. The main objection that can be raised against it is that it offers no explanation for the slow rate of hydrolysis of an alkyl nitrite in alkaline solution; the nitrite may be incapable of forming an addition complex with the alkali, but at the same time there seems little reason why the presence of the alkali should inhibit the formation of the postulated complex with water. It may also be urged that the nitrous esters do not stand entirely alone in their rapidity of hydrolysis; triphenylmethyl chloride, $\phi_3C \cdot Cl$, is hydrolysed just as fast and is very unlikely to form addition complexes with water or acids.

Thionitrites

The thionitrites are somewhat unstable compounds of the general formula $RS \cdot N:O$. They can be prepared by the action of a mercaptan on an alkyl nitrite at $-35°$, when an exchange takes place:[1]

$$EtON:O + EtSH \longrightarrow EtSN:O + EtOH.$$
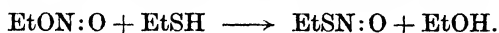
They are also formed by the action of nitrosyl chloride on mercaptans:[2]

$$EtSH + ClN:O \longrightarrow EtSN:O + HCl.$$
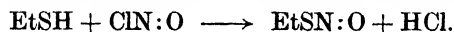
The latter reaction is best carried out at a low temperature and in an inert solvent because a variety of other reactions also takes place, notably the direct formation of the alkyl disulphide together with nitric oxide or hydroxylamine hydrochloride:

$$2RSH + 2ClN:O \longrightarrow RS \cdot SR + 2NO + 2HCl$$
$$4RSH + ClN:O \longrightarrow 2RS \cdot SR + NH_2OH,HCl.$$
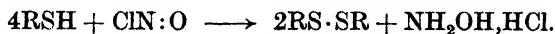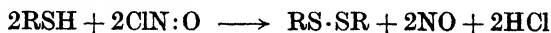
The simpler alkyl thionitrites are deep red liquids with a green reflection from their surface; they are sensitive to the oxygen of the air and in its presence decompose with evolution of nitrogen peroxide:

$$2RSN:O + O_2 \longrightarrow RS \cdot SR + N_2O_4.$$
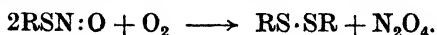
[1] H. Lecher and W. Siefken, *Ber.* 1926, **59**, 1314, 2594.

[2] H. S. Tasker and H. O. Jones, *J.C.S.* 1909, **95**, 1917; H. Rheinboldt, *Ber.* 1926, **59**, 1311; Rheinboldt *et al.*, *J. pr. Chem.* 1931, **130**, 133; 1932, **133**, 328.

They can be distilled unchanged under reduced pressure (EtSNO, boiling-point 19°/95 mm.) but those containing a primary or secondary alkyl group decompose slowly on heating into the disulphide and nitric oxide:

$$2RSN:O \longrightarrow RS \cdot SR + 2NO.$$

Thionitrites of higher molecular weight, such as triphenylmethyl thionitrite, $\phi_3CS \cdot N:O$, form green crystals at room temperature and are more stable. The thionitrites are much less soluble in water than the nitrites, but are miscible with all organic solvents. Their most surprising property is that, in contrast to the nitrites, they are 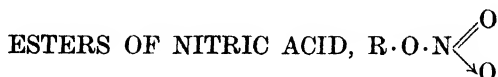very resistant to hydrolysis, not only by water, but also by aqueous acids and alkalis. This may arise from their insolubility in water, but investigation of their properties is difficult because of their instability.

ESTERS OF NITRIC ACID, $R \cdot O \cdot N \underset{O}{\overset{O}{\diagup}}$

The esters of nitric acid, like those of other mineral acids, can be prepared by the direct action of the acid upon the alcohols, but special precautions are required. The nitric acid generally contains nitrous acid, and in any case this is likely to be formed by the reduction of some of the nitric acid by the alcohol, and in the presence of nitrous acid the alcohol is violently oxidized, so that the yield is diminished and violent explosions may occur. The usual way to avoid this danger is to add urea which destroys the nitrous acid as it is formed:

$$CO(NH_2)_2 + 2HNO_2 \longrightarrow CO_2 + 2N_2 + 3H_2O.$$
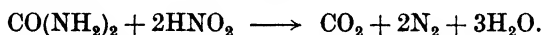
The nitric acid is first boiled with urea, then more urea is added and the alcohol added slowly. Another method of preparation which has been widely used for the nitric esters of the polyhydric alcohols is to add the alcohol at 0° to a mixture of concentrated nitric and sulphuric acids; after the reaction the whole is poured into water, when the nitric ester separates. The process resembles the nitration of an aromatic hydrocarbon, and for this reason glyceryl trinitrate is almost universally called nitroglycerine, whereas it is not a nitro compound at all, but an ester of nitric acid.

The lower alkyl nitrates are colourless, pleasant-smelling liquids whose boiling-points are not far removed from those of the corresponding alcohols and are considerably higher than those of the nitrites:

	Alcohol	Nitrite	Nitrate	Nitro compound
Methyl	65°	−12°	65°	101°
Ethyl	78°	+17°	88°	114°
n-Propyl . . .	96°	47°	111°	131°
iso-Propyl . . .	82°	45°	102°	120°
n-Butyl . . .	117°	75°	136°	151°

The high boiling-points of the alcohols are due to their association through the hydroxyl groups to more complex molecules. Association of this kind

cannot take place with the nitrates and the nitro compounds, but molecules of both types contain a coordinate link (semi-polar double bond), and the electric moment associated with such a link gives rise to large forces of attraction between the molecules, and hence leads to a smaller vapour pressure of the liquid.[1]

The alkyl nitrates burn with a white flame, and explode violently when heated above their boiling-points. On reduction with tin and hydrochloric acid they give the corresponding alcohols, showing that the nitrogen is attached to the carbon through oxygen; this is also proved by their hydrolysis by acids to alcohols and nitric acid, though these primary products may react with one another with the formation of aldehydes and nitrous acid. Hydrolysis of the nitrates of the polyhydric alcohols give a complicated mixture of products, especially if alkali is used. It has, however, been shown[2] that the first step is a true hydrolysis; thus if phosphoric acid is used, the alcohol formed combines with it and is protected from oxidation by nitric acid, the other primary product. The oxidation of the alcohol formed in the first stage takes place much more readily in presence of alkalis than of acids, and results in the formation of a variety of compounds. Aldehydes, hydroxy-acids, mesoxalic acid, oxalic acid, and carbon dioxide have been detected in the mixture obtained from glyceryl trinitrate and caustic potash. Nitrates, ammonia, and prussic acid are also found and are the reduction products of the nitrate groups.[3]

The alkyl nitrates condense with compounds containing a reactive methylene group in presence of sodium or potassium ethoxide to form *aci*-nitro compounds,[4] from which the true nitro compounds are obtained by the action of carbon dioxide (see p. 230):

$$EtO \cdot NO_2 + KOEt + \phi \cdot CH_2 \cdot CO_2Et \longrightarrow 2EtOH + \phi \cdot C(:NO \cdot OK) \cdot CO_2Et.$$
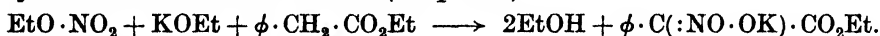
Ethyl nitrate reacts similarly with pyrroles and indoles which have a free β-position, to give the salt of the β-*aci*-nitro derivative from which the true nitro compounds can be obtained by the action of acids:[5]
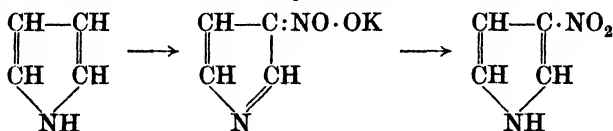
Like the alkyl nitrites, the esters of nitric acid react with excess of a Grignard reagent and, as the result of a complicated reaction, give an N-dialkylhydroxylamine.[6] Ethyl nitrate has been used as a nitrating agent for obtaining aromatic nitro compounds; the substance to be

[1] See A. E. van Arkel, *Trans. Faraday Soc.* 1934, **30**, 698.

[2] R. C. Farmer, *J.C.S.* 1920, **117**, 806.

[3] E. Berl and M. Delpy, *Ber.* 1910, **43**, 1421.

[4] W. Wislicenus *et al.*, *Ber.* 1902, **35**, 1755; 1909, **42**, 1930; 1910, **43**, 2234.

[5] A. Angeli, F. Angelico, *et al.*, *Atti R. Accad. Lincei*, 1902, **11**, 16; 1903, **12**, 344; 1904, **13**, 241; 1911, **20**, 311; *Gazz.* 1904, **34**, 57.

[6] H. Hepworth, *J.C.S.* 1921, **119**, 251.

nitrated is suspended or dissolved in concentrated sulphuric acid at $-5°$ and ethyl nitrate slowly added.[1]

The nitrates of certain of the polyhydric alcohols are of great importance in the explosive industry. Explosives are compounds or mixtures which undergo a very rapid decomposition and generate a large volume of heated gas, when they are subjected to some initiating disturbance such as heat, the mechanical impact of a solid or the explosion of some other compound. In almost all explosives the decomposition is an oxidation, the combined oxygen in the compound or mixture being roughly sufficient for the whole explosive to be transformed into gaseous products. The rate of the decomposition of an explosive determines the uses to which it can be put; if it is very high, an enormous pressure is produced almost instantaneously and the explosive, though useful as the filling for a high-explosive shell and for fracturing rock, cannot be used for propelling a bullet from a rifle or a shell from a gun. For these latter purposes a slower rate of decomposition is necessary, so that a gradually increasing pressure can give momentum to the projectile without fracturing the gun. Explosives are thus often divided into two classes, high explosives and propellents. The rate of decomposition depends not only on the chemical nature of the explosive, but also on its physical condition and the method whereby it is caused to explode. Some compounds, such as trinitro-toluene, show a high rate of decomposition under all conditions, so that they can only be used as high explosives; with others, such as certain nitric esters, the rate can be varied within limits by alterations in their physical state, and in consequence they can be used both as high explosives and as propellents.

The first of the nitric esters to be used as an explosive was glyceryl trinitrate, which for reasons given above is almost universally called nitroglycerine: its formula is

$$CH_2O \cdot NO_2$$
$$CHO \cdot NO_2$$
$$CH_2O \cdot NO_2.$$
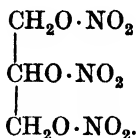
It is a colourless oily liquid which solidifies at $8°$, although it can be very considerably supercooled; it has been distilled at $25°$ under 0.0001 mm. pressure. When heated it explodes with great violence at a temperature of about $200°$, although it will burn rapidly but quietly at a lower temperature. The explosion can also be initiated by mechanical shock and by the explosion of a detonator containing mercuric fulminate. The compound was first manufactured on a large scale by Nobel in 1863 and quickly came into use, particularly for blasting in mining and quarrying. It has, however, many disadvantages; it is a liquid and is thus not easy to handle; for example, in blasting rock it may run out of the bore hole prepared for it into fissures in the rock and, escaping detonation, remain as a grave danger in further work. A more serious difficulty is that it solidifies above

[1] H. Raudnitz and H. Böhm, *Ber.* 1927, **60**, 738.

$0°$ and, when solid, is much less sensitive to detonators, so that it must be thawed before use, an operation which led to many accidents. Nobel overcame some of these difficulties in 1867 by his introduction of dynamite which consisted of nitroglycerine absorbed in kieselguhr, an absorbent infusorial earth. Kieselguhr dynamite is a plastic solid which can be packed in paper cartridges; it is less sensitive to shock than liquid nitroglycerine and has been widely used. The absorbed liquid solidifies at about $4°$, and in this state is difficult to detonate, so that it suffers from the same disadvantage as the liquid itself.

In the original dynamite the keiselguhr is a mere adsorbent and contributes nothing to the explosion, so that it is less efficient than pure nitroglycerine for blasting hard rock. This difficulty has been overcome by using adsorbent materials which are themselves either combustible or explosive and modern dynamites are all of one of these two types. Many preparations which have been used in quarrying consist essentially of a mixture of nitroglycerine and sodium or potassium nitrate together with wood pulp, starch, flour, or charcoal. They form powders which can be packed into waterproof cartridges. The most important discovery, however, was made by Nobel in 1875, when he found that nitroglycerine can be mixed with certain nitrocelluloses, with or without the assistance of a solvent, to give a plastic jelly which does not exude nitroglycerine and is unaffected by water. The product is called blasting gelatine and has been largely used for tunnelling through hard rock, but its action is too local and violent for many purposes. Suitable explosives for ordinary mining operations are made by mixing a thin blasting gelatine with a combustible absorbent mixture, such as can be obtained from potassium nitrate and wood pulp; these are all referred to as dynamites. Blasting gelatine is less sensitive to mechanical shock than kieselguhr dynamite, but freezes at low temperatures and is then much more sensitive and must be thawed before use. The difficulties and dangers caused by exposure of nitroglycerine preparations to low temperatures have been largely overcome in the non-freezing dynamites, in which a certain amount of glycol dinitrate is dissolved in the nitroglycerine so that the freezing-point is lowered. Glycol dinitrate, $CH_2(O \cdot NO_2) \cdot CH_2O \cdot NO_2$, is itself a more powerful explosive than nitroglycerine, so the efficiency of the dynamite is not reduced by such addition; it is, however, somewhat volatile, and this is its chief disadvantage.

The other class of nitric esters which are important as explosives are the derivatives of cellulose, usually called nitrocelluloses. Cellulose consists of a long chain of β-glucose units which are united by links through oxygen formed by loss of water between hydroxyl groups. Since each glucose molecule had originally five such groups and two are involved in the chain formation, there are three hydroxyl groups which can be esterified for every six carbon atoms, and if all these were combined with nitric acid, the formula of the cellulose nitrate would be $[C_6H_7O_2(ONO_2)_3]_n$, and its nitrogen content would be $14 \cdot 14$ per cent. The substances obtained by treating

cellulose, in the form of cotton, with a mixture of strong nitric and sulphuric acids do not contain as much nitrogen as this and are mixtures of partially nitrated celluloses. Their properties vary with the nitrogen content; the less nitrated substance, obtained by diluting the mixed acids with a little water, contains 11·5–12 per cent. of nitrogen and is soluble in a mixture of ether and alcohol, while that with a nitrogen content of 13 per cent. is insoluble in ether-alcohol, but readily soluble in acetone and ethyl acetate. The latter is called gun-cotton, and the former collodion-cotton or soluble nitrocellulose. That they are esters of nitric acid is shown by the facts that they are hydrolysed by alkalis to give nitric acid and that with reducing agents they split off the nitrate groups and are converted back into cellulose.

Soluble nitrocellulose can be detonated only with difficulty, and is of little value as an explosive: it has, however, other uses. Evaporation of its solution in ether-alcohol, which is known as collodion, leaves a firm continuous film, and on this property depended its use in surgery and the old wet-plate process of photography. A solution in molten camphor constituted celluloid, one of the first synthetic plastics, which, though not explosive, suffers from the disadvantage that it burns with great violence. Gun-cotton is used as an explosive for demolitions and military and naval purposes, as in torpedoes. In the fibrous state it explodes far too violently for use as a propellent in rifles or shotguns, but if the fibre structure is destroyed by dissolving it in a solvent, it can be obtained as a hard structureless mass which burns much more slowly on detonation; in this form it is the main constituent of the majority of smokeless powders which are used universally in guns of all sizes. Some of these contain nothing but gelatinized nitrocellulose in granular form together with a stabilizer which will unite with any decomposition products formed on storing the powder for a long time; the most dangerous of these products are oxides of nitrogen which catalyse further decomposition, but they cannot be neutralized by addition of alkali, because the alkali hydrolyses the nitric ester. The most widely used stabilizers are diphenylamine, which will combine with both nitric and nitrous acids, and the dialkyldiphenyl ureas, $O:C(NR\phi)_2$; these are called 'centralites' and are hydrolysed by traces of mineral acid to alkylanilines which remove the oxides of nitrogen. Other smokeless powders, such as the English military propellent cordite, consist essentially of nitrocellulose and a little nitroglycerine thoroughly gelatinized by mixing in a solvent which is afterwards removed. The rate of burning of the grains of smokeless powders is largely determined by their shape, so that by the choice of suitable shapes the propellent can be used for various types of guns.

Acyl Nitrates, $R \cdot CO \cdot O \cdot NO_2$

A further class of nitric acid derivatives are the acyl nitrates,[1] such as acetyl nitrate, $CH_3 \cdot CO \cdot ONO_2$, and benzoyl nitrate, $\phi \cdot CO \cdot ONO_2$. The

[1] F. E. Francis, *J.C.S.* 1906, **89**, 1; *Ber.* 1906, **39**, 3798; T. H. Butler, ibid. 3804; A. Pictet and E. Khotinsky, *C.r.* 1907, **144**, 210; *Ber.* 1907, **40**, 1163.

former is made by the action of nitrogen pentoxide on the acid anhydride, the latter by the action of silver nitrate upon the acid chloride at $-15°$. Acetyl nitrate is a fuming liquid, b.p. $22°/77$ mm. Benzoyl nitrate is a yellow oil.

They explode on sudden heating and resemble the acid chlorides in being rapidly decomposed by water into the organic acid and nitric acid. They are very powerful nitrating agents, and show a great tendency to give ortho-substituted products. Thus, for example, toluene and acetyl nitrate give 88 per cent. o- and 12 per cent. p-nitrotoluene.

Another mixed anhydride of acetic and nitric acids is the so-called diacetyl-orthonitric acid,[1] which is formed by the action of acetic anhydride on concentrated nitric acid, or of fuming nitric acid on acetic acid. It is a liquid boiling at $128°$, whose analysis and molecular weight indicate the generally accepted formula $(CH_3 \cdot CO \cdot O)_2 N(OH)_3$. This structure contains a penta-covalent nitrogen atom, and the constitution of the compound probably requires revision; it is doubtful whether the compound has been obtained in the pure condition. It is decomposed by water into acetic and nitric acids, and has found use as a nitrating agent. It reacts with acetic anhydride to give tetranitromethane (p. 246), and with acetanilide to give mainly o-nitroacetanilide,[2] while nitration of acetanilide with nitric acid in acetic acid gives almost exclusively the para-isomer.

[1] A. Pictet, *D.R.-P.* 1902, 137,100; A. Pictet, P. Genequand, and E. I. Klein, *Arch. Sci. phys. nat.* 1903, **15**, 589; **16**, 191; A. Pictet and P. Genequand, *Ber.* 1902, **35**, 2526.

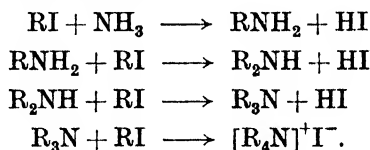[2] O. N. Witt and A. Utermann, *Ber.* 1906, **39**, 3901.

ALIPHATIC AMINES

THE aliphatic amino compounds can be considered as ammonia in which one, two, or three of the hydrogen atoms are replaced by monovalent aliphatic radicals. There are thus three classes, the primary amines, RNH_2, the secondary amines, R_2NH, and the tertiary amines, R_3N. Further, there are the quaternary ammonium compounds $[R_4N]^+X^-$, where the group $[R_4N]^+$ is a kation and X^- an anion such as Cl^-, HSO_4^-, or OH^-; these are analogous to the ammonium salts such as ammonium chloride, $[NH_4]^+Cl^-$. The groups attached to nitrogen in all four classes may be the same or different and may contain other reactive groups such as hydroxyl or carboxyl, so that a very large number of aliphatic amino compounds are known. Some occur in nature and play an important part in the constitution and physiology of living organisms.

Methods of Preparation

The more important methods of preparing aliphatic amines can be classified as follows:

1. *From ammonia.*

If an alkyl halide is treated with ammonia, a mixture of the primary, secondary, and tertiary amines is formed, together with a certain amount of the quaternary ammonium salt:

$$RI + NH_3 \longrightarrow RNH_2 + HI$$
$$RNH_2 + RI \longrightarrow R_2NH + HI$$
$$R_2NH + RI \longrightarrow R_3N + HI$$
$$R_3N + RI \longrightarrow [R_4N]^+I^-.$$

The ammonia is usually dissolved in alcohol, or sometimes water, and anhydrous liquid ammonia has also been used. Often the mixture must be heated, in which case the reaction is carried out in a sealed tube to prevent the loss of ammonia. The reaction was discovered by A. W. Hofmann in 1850, and is often called after him; by this method he was the first to prepare the secondary, tertiary, and quaternary compounds. Either the alkyl chloride, bromide, or iodide can be used, although the iodide usually reacts the most rapidly; a tertiary alkyl iodide, however, such as Me_3CI gives no amine but merely loses hydrogen iodide to form the olefine, e.g. $Me_2C:CH_2$. The ease with which the reaction takes place depends on the nature of the groups present in the halide molecule, and a compound such as chloracetic acid, $ClCH_2 \cdot CO_2H$, or chloromethyl ether, $ClCH_2 \cdot O \cdot CH_3$, reacts more rapidly than ethyl iodide. The proportions in which the four possible products are formed present a very complicated problem and

depend not only on the relative rates of reaction of the intermediate products, but also or the solubilities of the compounds in the solvent employed. In some cases a suitable selection of the conditions, solvent, temperature, duration of reaction and concentrations, can be found empirically which makes it possible to obtain one product almost exclusively, but often, as with ethyl iodide, all four possible products are produced and must afterwards be separated by physical or chemical means. Special methods of separation which have been used are mentioned below (p. 19).

Several modifications of Hofmann's original method have been used. The ammonia can be replaced by a primary or secondary amine and in this way secondary and tertiary amines containing different groups can be obtained. In place of the halide, the dialkyl sulphate can be used; since dimethyl sulphate is a commercial product, its action on a primary amine is a useful method for preparing a secondary methyl amine. Simple alkyl nitrates and sulphonates (p. 157) yield primary amines on treatment with ammonia. For preparing primary amines the compound of zinc chloride with ammonia is sometimes more convenient than a solution of ammonia.

The methylamines can be prepared from ammonia by the action of formaldehyde on an aqueous solution of ammonium chloride,[1] but the reaction is not general for other aldehydes. If the mixture is slowly distilled and the temperature is not allowed to exceed 104°, a good yield of methylamine hydrochloride can be obtained from the residue in the flask. If excess of formaldehyde is used at a higher temperature, di- and trimethylamines can be isolated. Formic acid, carbon dioxide, and methylal are also formed in the reaction, which probably involves the condensation of ammonia and formaldehyde followed by the reduction of the condensation product, or its anhydro derivative, by more formaldehyde.
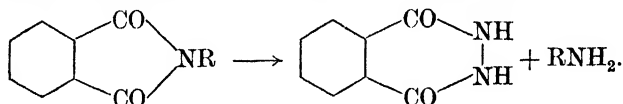
2. *From substitution-products of ammonia.*

To overcome the difficulty caused by the simultaneous production of all four classes of amines in the Hofmann reaction, S. Gabriel[2] introduced an ingenious general method for converting an aliphatic halide into the primary amine. The essence of the method is to avoid the formation of the other classes of amines by replacing ammonia with a compound in which there is only one hydrogen atom attached to nitrogen and which can be hydrolysed in the final stage of the reaction. The compound Gabriel chose was phthalimide because it is easily obtained. In the original form of the reaction the potassium derivative of phthalimide is heated with the alkyl halide and the resulting N-substituted phthalimide is hydrolysed by heating with a mineral acid to phthalic acid and a primary amine :

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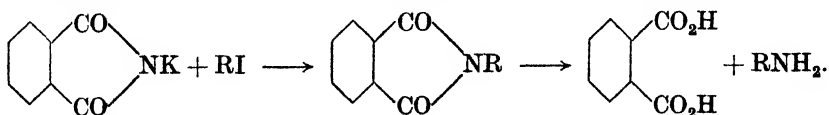
[1] J. Plöchl, *Ber.* 1884, **21**, 2117: E. A. Werner, *J.C.S.* 1917, **111**, 844.

[2] *Ber.* 1887, **20**, 2224.

The method has been of great value and can be used for the preparation of amines containing all kinds of other groups, such as amino-ketones, amino-nitriles, &c., but suffers from the disadvantage that in many cases the hydrolysis with acids is difficult and it is necessary to heat to a high temperature in a sealed tube. This difficulty has been overcome in the modified Gabriel reaction of H. R. Ing and R. H. F. Manske,[1] who have introduced two improvements. Firstly, they showed that the N-substituted phthalimide can be prepared by heating phthalimide with the aliphatic halogen compound in the presence of dry potassium carbonate; there is no need to use potassium phthalimide itself which is somewhat troublesome to prepare. Secondly, they found that the hydrolysis can be carried out very easily by the use of hydrazine. If the substituted phthalimide is warmed in alcoholic solution with hydrazine hydrate, and then hydrochloric acid added, it yields the hydrochloride of the desired amine and the insoluble hydrazide of phthalic acid which can be filtered off:

$$\text{(benzene ring)} \underset{CO}{\overset{CO}{<}} NR \longrightarrow \text{(benzene ring)} \underset{CO}{\overset{CO}{<}} \underset{NH}{\overset{NH}{|}} + RNH_2.$$

For the preparation of secondary alkylamines unaccompanied by the primary or tertiary compounds, the most convenient starting-point is technical calcium cyanamide which is used as a fertilizer (see p. 330).[2] This can be converted into the disodium salt of cyanamide by caustic soda, and the sodium salt reacts readily with alkyl halides to give the dialkyl-cyanamide which can be hydrolysed by heating with aqueous acids or alkalis. A mixture of the dialkylamine and ammonia can be distilled from the alkaline solution, and their separation usually presents no difficulty, since the lower volatile secondary amines form hydrochlorides which, unlike ammonium chloride, are soluble in chloroform, and the higher members are liquids which can be purified by distillation:

$$CaN \cdot CN \longrightarrow Na_2N \cdot CN \longrightarrow R_2N \cdot CN \longrightarrow R_2NH + CO_2 + NH_3.$$

Another class of substituted ammonia compounds which serve as a convenient source of certain alkylamines are the naturally occurring amino-acids. These on dry distillation with potassium hydroxide or baryta usually lose carbon dioxide smoothly to give either the amine or, if baryta is used, the carbonate of the amine:

$$R \cdot CH(NH_2) \cdot CO_2H \longrightarrow R \cdot CH_2 \cdot NH_2 + CO_2.$$
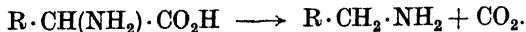
Thus pure iso-amylamine, $Me_2CH \cdot CH_2 \cdot CH_2 \cdot NH_2$, is prepared from leucine, an amino-acid which can be obtained by the hydrolysis of albumin.

3. *By the hydrolysis of other nitrogen compounds.*

These methods are not of great preparative importance. The first known aliphatic amine was prepared by A. Würtz in 1849 by the alkaline

[1] *J.C.S.* 1926, 2348.

[2] W. Traube and A. Engelhardt, *Ber.* 1911, **44**, 3149; E. B. Vliet, *J. Amer. C. S.* 1924, **46**, 1307.

hydrolysis of an alkyl isocyanate, which he obtained by treating an alkyl halide with silver cyanate:

$$RI + AgNCO \longrightarrow R \cdot N : C : O + AgI$$
$$R \cdot N : C : O + 2NaOH \longrightarrow RNH_2 + Na_2CO_3.$$
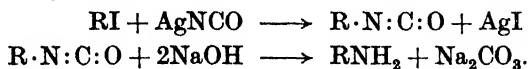
Similarly an isocyanide is hydrolysed very rapidly by aqueous mineral acids, to give a primary amine (see p. 318):

$$RNC + HCl + 2H_2O \longrightarrow RNH_2, HCl + H \cdot CO_2H.$$
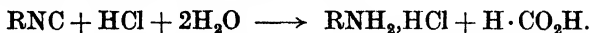
Aromatic amines in which there is a nitroso group in the para position to the amino group are hydrolysed by caustic alkalis to a nitrosophenol and an aliphatic amine (see p. 220). This provides a useful method for obtaining a secondary alkyl amine; for example, dimethylaniline forms a *p*-nitroso derivative with nitrous acid, and if the latter is boiled with aqueous caustic soda, pure dimethylamine is given off:

$$ON-\langle\bigcirc\rangle-NMe_2 + NaOH \longrightarrow ON-\langle\bigcirc\rangle-ONa + NHMe_2.$$
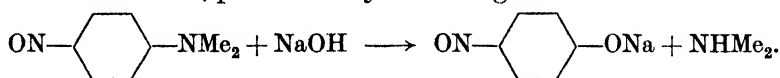
4. By the reduction of other nitrogen compounds.

A large variety of compounds can be reduced to amines. The reduction of nitro compounds, which is by far the commonest method of obtaining an aromatic amine, is not of much practical importance in the aliphatic series because of the difficulty of preparing aliphatic nitro compounds. On the other hand, the reduction of certain other classes of compounds is often of great value. The more important cases are the following:

(a) *Nitriles.* The reaction can be written

$$R \cdot C : N + 4H \longrightarrow R \cdot CH_2 \cdot NH_2,$$

and since the cyano compound is usually obtained with ease by boiling an alkyl halide with potassium or sodium cyanide, the method is of wide application. It was discovered by Mendius and is frequently called after him. The usual reducing agent is sodium in boiling alcohol, but hydrogen in the presence of nickel[1] at 180–220° or at room temperature in the presence of colloidal palladium[2] can be used. Often the primary base, which might be expected to be the sole product, is accompanied by the secondary base, $(RCH_2)_2NH$, and sometimes the tertiary base, $(RCH_2)_3N$, as well, especially in the catalytic reductions. These arise from secondary reactions of the imine formed as the first stage in the reduction:

$$R \cdot CN + 2H \longrightarrow R \cdot CH : NH.$$
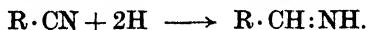
In the production of the secondary base the imine condenses with some of the primary amine already formed to give ammonia and a Schiff's base which is readily reduced to the secondary amine:[3]

$$R \cdot CH : NH + H_2N \cdot CH_2R \longrightarrow NH_3 + R \cdot CH : N \cdot CH_2R \longrightarrow (RCH_2)_2NH.$$
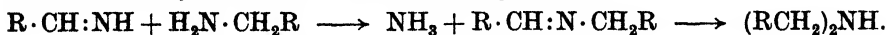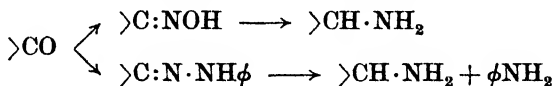
[1] P. Sabatier and J. B. Senderens, *C.r.* 1905, **140**, 482.

[2] A. Skita, *Ber.* 1909, **42**, 1627.

[3] J. von Braun, ibid. 1923, **56**, 1988; H. Rupe and E. Hodel, *Helv. Chim. Acta*, 1923, **6**, 865; K. Kindler, *Annalen*, 1931, **485**, 113; C. F. Winans and H. Adkins, *J. Amer. C. S.* 1932, **54**, 308.

The formation of secondary and tertiary amines can be avoided in the catalytic reduction by using platinum oxide as catalyst and acetic anhydride as solvent;[1] the primary amine is acetylated immediately it is formed and the reactions with the imine cannot take place. The amine is isolated as its acetyl derivative from which the acetyl group can be removed by hydrolysis.

(b) *Oximes and phenylhydrazones.* The reduction of both these classes of compounds gives primary amines and affords a simple method of introducing an amino group in the place of a carbonyl group. With the hydrazones the molecule is split between the two nitrogen atoms, as is the general rule in the reduction of compounds containing linked nitrogen atoms.

$$>CO \left< \begin{array}{l} >C:NOH \longrightarrow >CH \cdot NH_2 \\ >C:N \cdot NH\phi \longrightarrow >CH \cdot NH_2 + \phi NH_2 \end{array} \right.$$

Since both classes of compounds are hydrolysed by aqueous mineral acids, the reduction is usually carried out with sodium amalgam in acetic acid or, especially with oximes, by adding sodium to the hot alcoholic solution of the substance. Electrolytic reduction is also used, but many other reagents cause the nitrogen atom to be split off as ammonia. A somewhat similar method is the reduction of an aldehyde-ammonia, which takes place by the action of zinc dust and hydrochloric acid or electrolytically in acid solution:

$$R \cdot CH(OH) \cdot NH_2 \longrightarrow R \cdot CH_2 \cdot NH_2.$$

5. *By reactions which involve rearrangement.*

There are three interesting rearrangements which are used for the preparation of primary aliphatic amines. Two of them are degradations of derivatives of acids and make it possible to replace a carboxyl group by an amino group: $R \cdot CO_2H \longrightarrow R \cdot NH_2$.

(a) The first is Hofmann's rearrangement of an acid amide. The mechanism of the change is discussed later (p. 146). If an amide is treated with bromine and an aqueous caustic alkali or with a solution of sodium hypochlorite, the primary amine containing one carbon atom less than the amide is formed:

$$R \cdot CONH_2 + Br_2 + 2KOH \longrightarrow R \cdot NH_2 + 2KBr + CO_2 + H_2O.$$
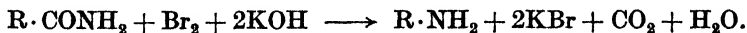
The amine, if volatile, can be distilled in steam from the reaction mixture and collected in dilute hydrochloric acid. It is accompanied by some ammonia formed by the direct hydrolysis of the amide. The amine hydrochloride can usually be separated from the ammonium chloride by extracting the mixture with alcohol in which ammonium chloride is hardly soluble. The reaction gives good yields with the amides of the lower fatty acids, but, as the number of carbon atoms in the molecule increases,

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[1] W. H. Carothers and G. A. Jones, ibid. 1925, 47, 3051; see also O. Schales, *Ber.* 1935, 68, 1943. [2] P. Knudsen, *Ber.* 1909, 42, 3994.

there is a greater tendency for some of the amine formed to be converted into the nitrile of the next lower acid, and thus the yield is decreased:
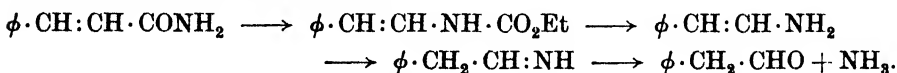
$$R \cdot CH_2 \cdot NH_2 + 2Br_2 \longrightarrow R \cdot CH_2 \cdot NBr_2 \longrightarrow R \cdot C\vdots N + 2HBr.$$

Thus Hofmann[1] found that amides containing up to six carbon atoms give 80–90 per cent. of the possible yield of amine, but that hexylamine is obtained in 70 per cent. yield and heptylamine in only 30 per cent.
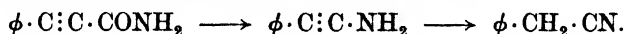
This difficulty can be avoided by carrying out the reaction with sodium methoxide in methyl alcohol or with alcoholic potash, when the isocyanate, which is an intermediate product (see p. 146), reacts with the alcohol to form a urethane which can be isolated and afterwards hydrolysed:[2]

$$RNCO + MeOH \longrightarrow RNH \cdot CO_2Me$$
$$RNH \cdot CO_2Me + H_2O \longrightarrow RNH_2 + CO_2 + MeOH.$$
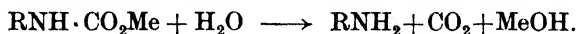
With certain classes of amides the Hofmann rearrangement does not give a primary amine. From an $\alpha\beta$-unsaturated amide the urethane derived from the amine can be obtained by working in alcoholic solution,[3] but if this is hydrolysed, the unsaturated amine is transformed into the imine which is further hydrolysed to an aldehyde and ammonia. Thus cinnamic amide gives phenylacetaldehyde:
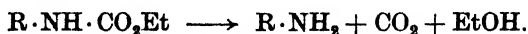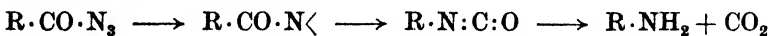
$$\phi \cdot CH\vdots CH \cdot CONH_2 \longrightarrow \phi \cdot CH\vdots CH \cdot NH \cdot CO_2Et \longrightarrow \phi \cdot CH\vdots CH \cdot NH_2$$
$$\longrightarrow \phi \cdot CH_2 \cdot CH\vdots NH \longrightarrow \phi \cdot CH_2 \cdot CHO + NH_3.$$

Similarly phenylpropiolic amide gives benzylcyanide:

$$\phi \cdot C\vdots C \cdot CONH_2 \longrightarrow \phi \cdot C\vdots C \cdot NH_2 \longrightarrow \phi \cdot CH_2 \cdot CN.$$

The Hofmann rearrangement of the amides of α-hydroxy acids is mentioned later.

(b) The Curtius degradation of the azide of an acid resembles the Hofmann rearrangement in that a carboxyl group is converted into a primary amino group. The mechanism of the reaction is discussed later (p. 377). The azide of any carboxylic acid loses nitrogen on heating with a readiness that depends on the nature of the acid; the free radical so formed rearranges to an isocyanate if in an inert solvent, and this can be hydrolysed to a primary amine and carbon dioxide. If, as is usually the case, the azide is heated in alcoholic solution, the product is the urethane formed by the addition of alcohol to the isocyanate. The urethane can be hydrolysed by mineral acids to the amine:

$$R \cdot CO \cdot N_3 \longrightarrow R \cdot CO \cdot N\langle \longrightarrow R \cdot N\vdots C\vdots O \longrightarrow R \cdot NH_2 + CO_2$$

$$\downarrow \text{EtOH}$$

$$R \cdot NH \cdot CO_2Et \longrightarrow R \cdot NH_2 + CO_2 + EtOH.$$

The reaction is a general one but has the disadvantage that some azides are explosive. An interesting modification is the action of hydrazoic acid

[1] Ber. 1882, 15, 762.   [2] E. Jeffreys, ibid. 1897, 30, 898.
[3] R. A. Weermann, Rec. trav. chim. 1907, 26, 203.

on a carboxylic acid in the presence of strong sulphuric acid, when carbon dioxide and nitrogen are evolved and the amine is formed (see p. 370):

$$R \cdot CO_2H + HN_3 \longrightarrow RNH_2 + CO_2 + N_2.$$
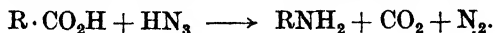
(c) The third rearrangement which can be used to obtain a primary amine is the Beckmann rearrangement of the ketoximes. When a ketoxime in dry ether is treated with a reagent such as phosphorus pentachloride, it is transformed into a substituted amide, which can be hydrolysed to a primary amine and an acid (see p. 177):

$$\underset{\text{NOH}}{R \cdot C \cdot R'} \longrightarrow \underset{\text{NHR}}{O:C \cdot R'} \longrightarrow R' \cdot CO_2H + RNH_2.$$
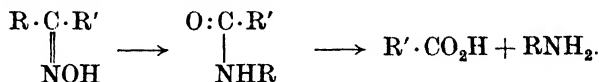
This reaction is not often used for the preparation of amines, but is occasionally useful. Thus pure methylamine free from ammonia cannot be obtained by many of the methods mentioned so far, because the salts of methylamine cannot be separated by crystallization from those of the ammonia which is formed at the same time. If acetoxime, however, is heated with sulphuric and acetic acids, methyl acetamide, $CH_3 \cdot CO \cdot NHMe$, is formed and can be hydrolysed to pure methylamine.[1]

Separation of Four Classes of Amines

Since several of the methods of preparation which have been described give mixtures of amines, to obtain a single compound involves its separation from the other amines formed. Primary, secondary, and tertiary amines can be easily separated from the quaternary salts by distillation from alkaline solution, since the quaternary hydroxides are not volatile and remain behind. For the separation of the primary, secondary, and tertiary compounds, a variety of methods have been used in different cases. Sometimes, as with the ethylamines, continued fractional distillation is satisfactory.[2] In other cases advantage can be taken of the differing solubilities of the salts of the three compounds in a solvent; thus the hydrochlorides of dimethylamine and trimethylamine are easily soluble in chloroform, while that of methylamine is insoluble. One amine can often be obtained pure by chemical means: for example, a secondary amine can be freed from a primary amine by the reactions with nitrous acid which are described below, and a tertiary amine can be separated from primary and secondary amines by treating the mixture with acetic anhydride, when the tertiary amine is unattacked and the other two amines are acetylated to give non-basic amides.

In addition to these special methods one chemical method is known which is of wide application: it was discovered by O. Hinsberg.[3] The mixed primary, secondary, and tertiary bases are treated with benzene sulphonyl chloride in the presence of aqueous caustic potash. The tertiary

[1] O. Wallach, *Annalen*, 1900, **312**, 175, footnote.
[2] W. E. Garner and D. Tyrer, *J.C.S.* 1916, **109**, 174.
[3] *Ber.* 1890, **23**, 2963; 1905, **38**, 906.

base contains no hydrogen atom attached to nitrogen and hence does not react with the acid chloride, while the other two amines give substituted sulphonamides which are not volatile, and thus the tertiary can be obtained pure by steam distillation. The two sulphonamides, of formula $\phi \cdot SO_2 \cdot NHR$ and $\phi \cdot SO_2 \cdot NR_2$ respectively, differ in that the derivative of the primary amine contains a hydrogen atom attached to nitrogen and is a weak acid (see p. 157), while the secondary derivative shows no acid properties. Hence the primary sulphonamide is soluble in aqueous alkali while the secondary compound is not and the two can be separated. The amines can be recovered from the sulphonamides by hydrolysis with mineral acids, but the reaction does not take place readily and in many cases the sulphonamide must be heated with hydrochloric acid to 150–160° in a sealed tube. The separation fails in the case of very weakly basic amines since these do not react with the acid chloride. p-Toluene sulphonyl chloride, which is obtained as a by-product in the manufacture of saccharine (see p. 158), can be used in place of the benzene derivative.[1] In some cases the primary amine reacts with two molecules of sulphonyl chloride to give the disulphonamide $(\phi \cdot SO_2)_2 NR$, which is naturally insoluble in alkali. This difficulty is overcome by boiling the sulphonamides with sodium methoxide in methyl alcohol when the disulphonamide is hydrolysed to the mono-amide.

Occurrence and Properties of the Alkylamines

The lower aliphatic amines are gases or volatile liquids: they are very soluble in water and have a smell which recalls that of ammonia but is somewhat fishy and unpleasant. Their vapours burn readily in air and it was by this property that Würtz realized that the gas he obtained from ethyl isocyanate was not ammonia, as he had at first supposed. The higher members (from undecylamine, $C_{11}H_{23} \cdot NH_2$, m.p. 16·5°, upwards) are solids and, as the molecular weight increases, the smell and solubility in water diminish. The primary amines which contain a long carbon chain, such as heptadecylamine, $C_{17}H_{35} \cdot NH_2$, resemble the paraffin hydrocarbons rather than ammonia in their physical properties, and the influence of the carbon chain is also shown by the fact that their hydrochlorides are insoluble in water but easily soluble in alcohol. The boiling-points of some typical amines are as follows:

R			RNH_2	R_2NH	R_3N
Methyl	.	.	.	$-6°$	$+7°$	$+3\cdot5°$
Ethyl	.	.	.	$+16\cdot5°$	56°	89°
Propyl	.	.	.	49°	110°	156°
iso-Propyl	.	.	.	32°	84°	..
iso-Amyl	.	.	.	96°	186°	237°
n-Octyl	.	.	.	179°	297°	366°

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[1] G. R. Clemo and W. H. Perkin, *J.C.S.* 1922, **121**, 648, footnote.

The alkylamines are markedly basic and their aqueous solutions are alkaline to litmus; those which are sufficiently non-volatile absorb carbon dioxide from the air to give crystalline carbonates. In these respects they differ from the compounds where the amino group is attached to an aromatic nucleus. The dissociation constants of the alkylamines are discussed below (p. 30). They form stable salts with most acids and nearly all of those derived from the simpler amines are freely soluble in water. These salts are distinguished from the ammonium salts by being soluble in alcohol, a fact which is sometimes used to effect a partial separation of an amine from ammonia. The salts in general resemble those of ammonium and, as with that kation, the platinichloride (e.g. $(RNH_3)_2PtCl_6$), the aurichloride (e.g. RNH_3AuCl_4), and the perchlorate are usually the least soluble and are often used for the separation of small quantities of an amine. The platinichlorides can be used for the determination of the molecular weight of an organic base, since on ignition they leave nothing but a residue of pure platinum which can be weighed. Many alkylamines form sparingly soluble derivatives with certain nitro compounds, and these are useful for the identification of the amines; examples of such nitro compounds are picric acid (2,4,6-trinitrophenol), styphnic acid (trinitro-resorcinol), and picrolonic acid; the latter is obtained by nitration of 1-phenyl-3-methyl-pyrazolone, a compound used in the manufacture of certain drugs and dyes, and it has the formula:

$$NO_2 \!-\!\!\!\bigcirc\!\!\!-\!N \!\!<\!\! \begin{array}{c} N\!-\!C\cdot Me \\ | \\ CO\!-\!CH\cdot NO_2. \end{array}$$
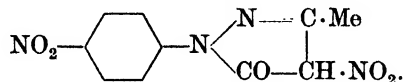
A number of abnormal salts of the aliphatic amines, such as a dihydrochloride of dimethylamine, have been described; these have usually been obtained by treating the amine with gaseous hydrogen chloride. The majority of these substances are not definite compounds, since the content of hydrogen chloride varies continuously with the temperature and only at certain arbitrary temperatures does the amount of hydrogen chloride absorbed correspond to a simple compound.[1] Hydrofluoric acid, however, in 48 per cent. aqueous solution gives abnormal hydrofluorides with many organic bases, all of which are of the type, Base, 4HF.[2] Many of these can be sublimed without decomposition.

Of the simpler aliphatic amines, mono-, di-, and trimethylamine, iso-butylamine, $Me_2CH\cdot CH_2\cdot NH_2$, and isoamylamine, $Me_2CH\cdot CH_2\cdot CH_2\cdot NH_2$, but no others, have been detected as products of plant and animal life. In many cases they are not produced in the normal metabolism but are secondary products arising from the decomposition of normal products; thus the two latter amines are formed by bacterial action (decarboxylation) on the amino-acids valine and leucine. In other cases, however, they seem to be primary products; thus methylamine and trimethylamine are

[1] W. H. Hunter and G. D. Byrkit, *J. Amer. C. S.* 1932, **54**, 1948.
[2] J. F. Berliner and R. M. Hann, *J. Phys. Chem.* 1928, **32**, 1142.

found in the roots of the sweet flag (*Acorus calamus* L.), in several species of *Chenopodium* and in the leaves and seeds of dog's mercury (*Mercurialis perennis* L.). Trimethylamine is widely spread in the plants and also in the tissues and excreta of fishes; brine in which herrings have been cured contains appreciable quantities of this base. Its source appears to be the break-down of choline:
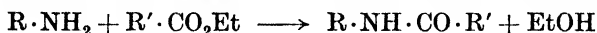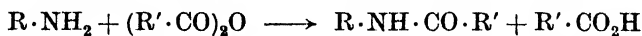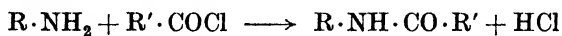
$$CH_2OH \cdot CH_2 \cdot NMe_3 \ [OH] \longrightarrow CH_2OH \cdot CH_2OH + NMe_3.$$
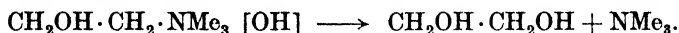
Trimethylamine and its oxide, $Me_3N \rightarrow O$, are among the forms in which fish excrete superfluous nitrogen; those which live in rivers contain very little of these compounds in their tissues, but the blood of the sharks and sea-fish has been found to contain much more. The distinction is probably due to the retention of the waste products by the sea-dwellers in order to raise the osmotic pressure of their body-fluids to that of the medium in which they live.[1] Trimethylamine can be obtained by the distillation of beet-sugar molasses, when it is formed by the decomposition of betaine, $\overset{+}{Me_3N} \cdot CH_2 \cdot CO_2^-$ (see p. 123).

The Chemical Properties of the Alkylamines

The chemical behaviour of the aliphatic amines differs in several respects from that of a compound such as aniline, in which the amino group is directly attached to an aromatic system. Amines such as benzylamine, $\phi CH_2 \cdot NH_2$, in which the amino group is in the side chain, show exactly the same chemical properties as the purely aliphatic amines. The primary and secondary bases contain hydrogen attached to the amino nitrogen atom and, in consequence, are attacked by many reagents to which the tertiary compounds are inert. The following are some of the more important reactions of this type:

1. *Acylation.* Primary and secondary amines react vigorously with acid chlorides, less vigorously with acid anhydrides, and slowly with esters to give their acyl derivatives, which are N-substituted amides. These reactions are discussed later (p. 138).

$$R \cdot NH_2 + R' \cdot COCl \longrightarrow R \cdot NH \cdot CO \cdot R' + HCl$$
$$R \cdot NH_2 + (R' \cdot CO)_2O \longrightarrow R \cdot NH \cdot CO \cdot R' + R' \cdot CO_2H$$
$$R \cdot NH_2 + R' \cdot CO_2Et \longrightarrow R \cdot NH \cdot CO \cdot R' + EtOH$$

The tertiary amines cannot give products of this type; they are unaffected by anhydrides or esters, but combine with acid chlorides to give unstable quaternary compounds of the type $R_3N \cdot CO \cdot R'[Cl]$.

2. *Nitrous acid.* The behaviour of the three classes of amines towards nitrous acid is very characteristic and serves as a means of distinguishing them. The reaction is usually carried out by dissolving the base in dilute hydrochloric acid, or dissolving its hydrochloride in water, and adding

[1] F. A. Hoppe-Seyler, *Z. Biologie*, 1930, **90**, 433.

an aqueous solution of sodium nitrite. The tertiary bases do not react at all.

The secondary amines give a nitrosamine, no nitrogen being evolved:

$$R_2NH + HONO \longrightarrow R_2N \cdot NO + H_2O.$$
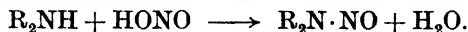
The lower nitrosamines are colourless volatile liquids which are soluble in water, while those of higher molecular weight are insoluble. They are not basic and can be reconverted into the secondary amines by simple means (see p. 452) and hence they are sometimes used in order to separate a secondary amine from primary and tertiary bases.

The primary aliphatic amines are converted by nitrous acid into alcohols, nitrogen being evolved. The reaction can be represented by the following equation, but is more complicated in its mechanism:

$$RNH_2 + O:NOH \longrightarrow ROH + N_2 + H_2O.$$
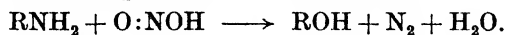
Only in a few exceptional cases (see p. 349) is there any indication of the intermediate formation of a diazo compound of the structure $R \cdot N : N \cdot OH$ or $[R \cdot N : N]^+ X^-$, which is the product of the action of nitrous acid on an aromatic primary amine. The complexity of the reaction is shown by the facts that a certain amount of an olefine is always formed, such as propylene, $CH_3 \cdot CH : CH_2$, from propylamine, and that sometimes during the reaction quite profound changes take place in the structure of the molecule and an alcohol is obtained which does not correspond to the amine. Thus Henry found[1] that normal propylamine, $CH_3 \cdot CH_2 \cdot CH_2 \cdot NH_2$, gives 42 per cent. of normal propyl alcohol, $CH_3 \cdot CH_2 \cdot CH_2OH$, and 58 per cent. of isopropyl alcohol, $CH_3 \cdot CHOH \cdot CH_3$, in which the hydroxyl group is attached to a different carbon atom from that which carried the amino group; similarly isobutylamine, $Me_2CH \cdot CH_2 \cdot NH_2$, gives 75 per cent. of trimethylcarbinol, $Me_3C \cdot OH$, and only 25 per cent. of isobutyl alcohol. D. W. Adamson and J. Kenner[2] have shown that with increase in the number of carbon atoms in the molecule the amount of secondary alcohol obtained decreases rapidly; n-octylamine gives only 5 per cent. of sec-octyl alcohol, and n-nonyl- and decylamines no secondary alcohol at all. On the other hand the amount of olefine formed (about 25 per cent. of the amine) remains fairly constant.

The rearrangements that take place in saturated cyclic compounds, which are, of course, alkylamines, are even more surprising in view of the fact that the reaction proceeds in dilute aqueous solution at about room temperature. With cyclopropylamine the ring is opened and the main product is allyl alcohol.[3]
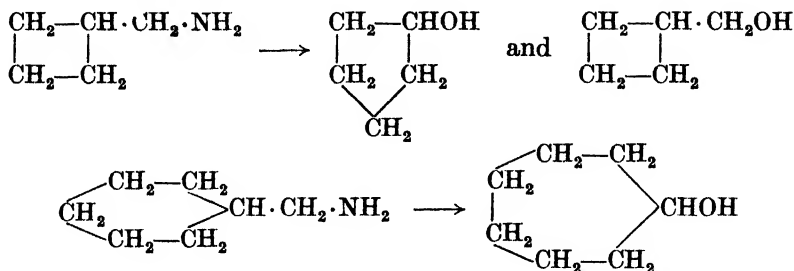
$$\begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix} \Big\rangle CH \cdot NH_2 \longrightarrow CH_2 : CH \cdot CH_2OH$$
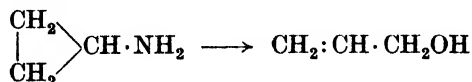
Enlargement of the ring can occur with the higher cycloparaffins; cyclo-butylmethylamine gives cyclopentanol as well as the cyclobutyl carbinol

[1] *C.r.* 1907, **145**, 899, 1247.   [2] *J.C.S.* 1934, 838.
[3] N. Kishner, *J. Russ. Phys. Chem. Soc.* 1905, **37**, 304; *Zent.* 1905, i, 1704.

and the corresponding olefines, and cyclohexylmethylamine gives cyclo-heptanol and cycloheptene.[1]

$$\begin{array}{c} \text{CH}_2\text{—CH·CH}_2\text{·NH}_2 \\ | \qquad | \\ \text{CH}_2\text{—CH}_2 \end{array} \longrightarrow \begin{array}{c} \text{CH}_2\text{—CHOH} \\ | \qquad | \\ \text{CH}_2 \quad \text{CH}_2 \\ \diagdown\diagup \\ \text{CH}_2 \end{array} \quad \text{and} \quad \begin{array}{c} \text{CH}_2\text{—CH·CH}_2\text{OH} \\ | \qquad | \\ \text{CH}_2\text{—CH}_2 \end{array}$$

$$\begin{array}{c} \text{CH}_2\text{—CH}_2 \\ \text{CH}_2 \qquad \diagdown \\ \diagdown\text{CH}_2\text{—CH}_2 \diagup\text{CH·CH}_2\text{·NH}_2 \end{array} \longrightarrow \begin{array}{c} \diagup\text{CH}_2\text{—CH}_2 \\ \text{CH}_2 \qquad \diagdown \\ | \qquad\qquad \text{CHOH} \\ \text{CH}_2 \qquad \diagup \\ \diagdown\text{CH}_2\text{—CH}_2 \end{array}$$
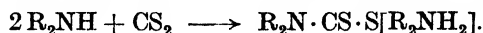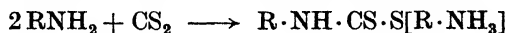
Little is known of the mechanism underlying these striking rearrangements. The reaction between aliphatic amines and nitrous acid has been shown[2] to be of the third order: it is not a simple decomposition of the amine nitrite but, both for primary and secondary amines, the velocity varies as the product $[\text{RNH}_3^+][\text{NO}_2^-][\text{HNO}_2]$. A reaction-complex is formed consisting of the amine nitrite and a molecule of nitrous acid, the latter being liberated unchanged in the decomposition of the reaction-complex. Until the role of this apparently unnecessary molecule of nitrous acid is understood, the problem of the mechanism of the reaction can hardly find a satisfactory solution.

Nitrosyl chloride, NOCl, behaves towards the amines in a manner similar to that of nitrous acid. With secondary bases nitrosamines are formed, and with primary bases nitrogen is evolved and the amino group is replaced by chlorine.[3] Profound structural rearrangement sometimes occurs in the latter reaction.

$$\text{R}_2\text{NH} + \text{ClN:O} \longrightarrow \text{R}_2\text{N·NO} \qquad \text{RNH}_2 + \text{O:NCl} \longrightarrow \text{RCl} + \text{N}_2 + \text{H}_2\text{O}$$

3. *Carbon disulphide.* Both primary and secondary amines react with carbon disulphide in alcoholic solution to give alkyldithiocarbamic acids which combine with more of the amine to form the salt:

$$2\,\text{RNH}_2 + \text{CS}_2 \longrightarrow \text{R·NH·CS·S[R·NH}_3]$$
$$2\,\text{R}_2\text{NH} + \text{CS}_2 \longrightarrow \text{R}_2\text{N·CS·S[R}_2\text{NH}_2].$$

Tertiary amines do not react and under suitable conditions the aromatic amines react differently (see p. 51). The dithiocarbamic acids derived from the primary and secondary bases differ in that certain metallic salts of the former decompose in boiling water to give an alkyl isothiocyanate or mustard oil:

$$\text{R·NH·CS·SHgCl} \longrightarrow \text{HgS} + \text{HCl} + \text{R·N:C:S}.$$

[1] O. Wallach, *Annalen*, 1907, **353**, 327; N. Demjanov and M. Luschnikov, *J. Russ. Phys. Chem. Soc.* 1903, **35**, 26; 1904, **36**, 166; *Zent.* 1904, i, 1214; L. Ruzicka and W. Brugger, *Helv. Chim. Acta*, 1926, **9**, 399.

[2] T. W. J. Taylor, *J.C.S.* 1928, 1099, 1897; Taylor and L. S. Price, *J.C.S.* 1929, 2052.

[3] W. Solonina, *Zent.* 1898, ii. 887.

The mustard oils (see p. 337) are volatile liquids of a sharp characteristic odour and their formation constitutes Hofmann's 'mustard-oil reaction' for detecting primary amines.

4. *Carbylamine reaction.* A primary amine when heated with chloroform and alcoholic potash gives an isocyanide or carbylamine; neither secondary nor tertiary amines show this behaviour. Since the carbylamines (see p. 317) have a characteristic, powerful and repulsive smell, the reaction can be used to detect the presence of a primary amine, a very small quantity of the substance being sufficient for the test.

$$R \cdot NH_2 + CHCl_3 + 3KOH \longrightarrow R \cdot NC + 3KCl + 3H_2O$$
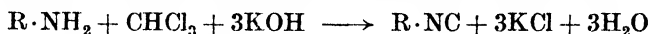
5. *Grignard reagents.* Primary and secondary amines react at room temperature with methyl magnesium iodide evolving methane and giving compounds in which one hydrogen atom of the amino or imino group is replaced:

$$R \cdot NH_2 + CH_3 \cdot MgI \longrightarrow R \cdot NH \cdot MgI + CH_4.$$
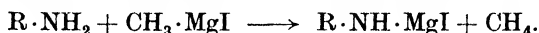
The reaction is the basis of T. Zerewitinov's method[1] for the estimation of amino and imino groups. If the conditions are carefully controlled, the volume of methane evolved is a measure of the amount of these two groups present in a compound. At higher temperatures the derivative of a primary amine reacts with a further molecule of methyl magnesium iodide evolving another equivalent of methane and forming a derivative $R \cdot N(MgI)_2$. This fact can be used to estimate the number of amino groups in a compound which is both a primary and a secondary amine, but corrections must be applied for the amount of methane formed in the spontaneous decomposition of the Grignard reagent when heated. The magnesium compounds formed by these reactions are decomposed by water to give the original amine.

Tertiary amines form addition compounds with Grignard reagents to give complexes which resemble those formed between ethers and Grignard compounds. Their composition varies from case to case and some crystalline complexes are known which contain both a tertiary amine and an ether.

The most characteristic reaction of tertiary amines which is not shown by either the primary or secondary bases is their union with alkyl halides or sulphates to form quaternary ammonium salts.
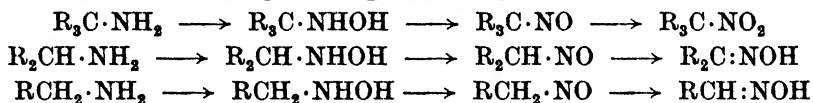
$$R_3N + MeI \longrightarrow [R_3NMe]I.$$
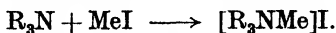
This is discussed in detail below (p. 27).

The oxidation of aliphatic amines gives rise to a large variety of products according to the constitution of the amine and the oxidizing agent employed. In acid solution the large majority of amines are very resistant to oxidation, but in alkaline solution the primary, secondary, and tertiary bases are usually attacked with ease. In their behaviour towards the amino group oxidizing agents can be divided into two classes.[2] The first

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[1] *Ber.* 1907, **40**, 2023; 1908, **41**, 2233.
[2] S. Goldschmidt and V. Voeth, *Annalen*, 1924, **435**, 265.

class includes persulphuric acid, Caro's acid (permonosulphuric acid), peracetic acid, benzoyl peroxide, $(\phi \cdot CO)_2O_2$, and hydrogen peroxide, and their first action is to give oxygen up to the nitrogen atom of the amino group; the second class, of which potassium permanganate and lead dioxide are important examples, remove hydrogen from the amino group to give a free radical which subsequently undergoes various transformations. The evidence for this generalization comes mainly from the behaviour towards oxidizing agents of the aromatic amines, such as aniline (see p. 53), but it gives a ready explanation of the products formed in the oxidation of the aliphatic bases. The primary product with a reagent of the first class is the amine oxide formed by addition of oxygen. If the base is tertiary, the amine oxide is stable and can often be obtained in good yield: $R_3N \longrightarrow R_3N \rightarrow O$. The amine oxides are discussed later (p. 166). If the base is secondary, the amine oxide rearranges to a di-N-substituted hydroxylamine, $R_2NH \rightarrow O \longrightarrow R_2NOH$, and the oxidation is often a good method for obtaining hydroxylamines of this type (see p. 164). If the base is primary, the same rearrangement takes place, and the hydroxylamine $R \cdot NHOH$ can sometimes be obtained in small yield; such hydroxylamines, however, are themselves easily oxidized and the main products are usually those formed by further oxidation. They include the nitroso and nitro compounds which can be separated as such if the primary amine group is attached to a tertiary carbon atom; in other cases the nitroso compound rearranges to an oxime (an aldoxime, if the carbon atom is primary, a ketoxime if it is secondary) and this may undergo further oxidation leading to complete disruption of the molecule.

$$R_3C \cdot NH_2 \longrightarrow R_3C \cdot NHOH \longrightarrow R_3C \cdot NO \longrightarrow R_3C \cdot NO_2$$
$$R_2CH \cdot NH_2 \longrightarrow R_2CH \cdot NHOH \longrightarrow R_2CH \cdot NO \longrightarrow R_2C:NOH$$
$$RCH_2 \cdot NH_2 \longrightarrow RCH_2 \cdot NHOH \longrightarrow RCH_2 \cdot NO \longrightarrow RCH:NOH$$

Oxidizing agents of the second class do not give products of these types. They have little action on tertiary amines except under conditions which are so violent that the whole molecule is disrupted.[1] With primary amines, the radical formed by loss of hydrogen usually rearranges to an imine which has been isolated in a few cases:[2]

$$RCH_2 \cdot NH_2 \longrightarrow RCH_2 \cdot N< \longrightarrow RCH:NH.$$

The imine is very readily hydrolysed to ammonia and a carbonyl compound, so that in most cases the product is an aldehyde or ketone or its further oxidation products.

$$RR'C:NH \longrightarrow RR'CO + NH_3$$
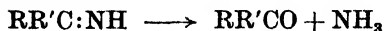
With secondary amines, there is evidence that the radical first polymerizes to a tetra-substituted hydrazine which may then undergo further changes.[3]

The last reaction of the alkylamines which will be mentioned is that in

[1] D. Vorländer, G. Blau, and T. Wallis, *Annalen*, 1906, **345**, 251.
[2] S. Goldschmidt and W. Beuschel, ibid. 1926, **447**, 197.
[3] S. Goldschmidt and V. Voeth, ibid. 1924, **435**, 265.

which an alkyl group is lost. If the hydrochloride of an amine is distilled at a high temperature, an alkyl chloride splits off and by this means a tertiary amine can be converted into a secondary base and the latter into a primary base. The methyl group, if present, is usually eliminated preferentially:

$$[Me_3NH]Cl \longrightarrow Me_2NH + MeCl.$$
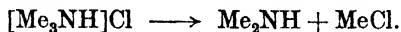
The reaction is the converse of Hofmann's synthesis. Methyl chloride is prepared technically in this way from the trimethylamine from beet sugar residues. A similar reaction takes place when highly alkylated bases are heated with concentrated hydrochloric acid or hydriodic acid to 200–300°. On this fact is based the Herzig-Meyer method of estimating the methylimino group (:NMe) in natural products such as alkaloids. The method resembles that of Zeisel for the estimation of the methoxyl group (·OMe); a weighed amount of the compound to be analysed is heated with strong hydriodic acid and the methyl iodide evolved estimated as silver iodide. In most cases the methoxyl group is attacked at a much lower temperature than the methylimino group, and the method can be used to distinguish between the two groups, but several compounds are known in which the methylimino group reacts at a low temperature, so that caution must be exercised.[1] Tertiary bases can also be converted into secondary amines by means of cyanogen bromide, a reaction discussed on p. 328.

The Quaternary Ammonium Compounds

When an alkyl halide is mixed with a tertiary aliphatic amine, direct addition takes place and a tetra-substituted ammonium salt is formed; thus trimethylamine and methyl iodide give tetramethylammonium iodide:

$$NMe_3 + MeI \longrightarrow [NMe_4]I.$$

The compounds obtained from the methyl or ethyl halides are sometimes described as the methiodide, ethochloride, and so on, of the tertiary base, especially if the latter has a trivial name of its own. Similarly dimethyl sulphate reacts with a tertiary base to give the 'methosulphate', which is the tetra-substituted ammonium salt of methyl hydrogen sulphate, $[R_3NMe]O \cdot SO_2 \cdot OMe$. These reactions often take place vigorously with evolution of heat, but proceed with very different ease in different cases; sometimes it is necessary to heat the two components together. The velocity of the reaction has been measured in several cases and this is one of the best known cases of a bimolecular reaction in solution.[2] The velocity varies enormously with the solvent employed; it is nearly 800 times as great in benzyl alcohol as in hexane. The high velocities in certain solvents must be due to some catalytic action of those solvents, since the velocity in the gas phase is of the same order of magnitude as that in the solvents

[1] See M. Busch, *Ber.* 1902, **35**, 1565; A. Kirpal, ibid. 1908, **41**, 819.

[2] For references and a full discussion see *Kinetics of Reactions in Solution*, E. A. Moelwyn-Hughes, Oxford, 1933, p. 106 et seq.

where the reaction is slow.[1] Both in the gas phase and in the 'slow' solvents, the reaction belongs to the class where the rate is several million times smaller th .n that predicted by the theory of bimolecular reactions.[2]

The quaternary ammonium salts have all the physical properties of salts; they are crystalline solids, soluble in water to give conducting solutions. They often show no precise melting-point, but decompose on heating; the halides usually give a tertiary amine and an alkyl halide, the smallest alkyl group present being eliminated:

$$[Et_2NMe_2]Cl \longrightarrow Et_2NMe + MeCl.$$
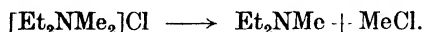
The hydroxides corresponding to these salts can best be obtained by treating the iodide in aqueous solution with excess of moist silver oxide, and evaporating the filtered solution *in vacuo*. Alternatively the chloride of the base is treated with potassium hydroxide in methyl alcohol, the insoluble potassium chloride removed and the methyl alcohol evaporated. In their physical properties they resemble the hydroxides of sodium and potassium. They are deliquescent white crystalline solids which are very readily soluble in water and are strong bases.

The quaternary ammonium hydroxides decompose when heated. Tetramethyl ammonium hydroxide gives trimethylamine and methyl alcohol, $[NMe_4]OH \longrightarrow NMe_3 + MeOH$, and although this type of decomposition takes place to some extent in other cases, the large majority of quaternary hydroxides give a tertiary amine, water, and an olefine:

$$[NEt_4]OH \longrightarrow NEt_3 + H_2O + CH_2:CH_2.$$

This reaction, which was discovered by Hofmann, has found important applications in the preparation of olefines and in the elucidation of the structure of complex bases; in the latter case it is usually called 'exhaustive methylation', since the base is methylated with methyl iodide up to the quaternary stage and the corresponding hydroxide is decomposed. Repetition of the process removes the nitrogen atom from a saturated cyclic amine and leaves the carbon skeleton; thus pyrrolidine is converted into butadiene.
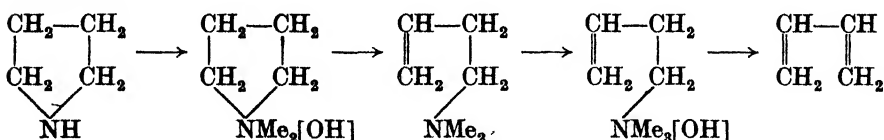

The products obtained in the decomposition of quaternary hydroxides and the ease with which the reaction proceeds vary with the nature of the groups attached to nitrogen.[3] The formation of an olefine involves the carbon atom next but one to the nitrogen, so that if this carbon atom carries no hydrogen atom, an olefine is often not formed, but an alcohol

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[1] E. A. Moelwyn-Hughes and C. N. Hinshelwood, *J.C.S.* 1932, 230.
[2] See Moelwyn-Hughes, loc. cit.
[3] W. Hanhart and C. K. Ingold, *J.C.S.* 1927, 997.

eliminated; thus benzyltrimethylammonium hydroxide gives benzyl alcohol:

$$[\phi \cdot CH_2 \cdot NMe_3]OH \longrightarrow \phi \cdot CH_2OH + NMe_3.$$
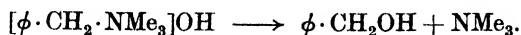
With other compounds of this class more profound structural change takes place during the decomposition. If the necessary hydrogen atom is present, olefine formation usually predominates. Certain olefines are liberated with great ease; quaternary hydroxides containing the group $O_2N \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot$ cannot be isolated since they decompose at room temperature to form nitrostyrene, $O_2N \cdot C_6H_4 \cdot CH:CH_2$. If the four alkyl groups are different, so that different olefines might be produced, the general rule is that an ethyl group will be eliminated as ethylene in preference to any other. Sometimes the olefine formed may be an isomer of that expected owing to the wandering of a double bond (see p. 539).

The structure of the quaternary ammonium compounds is of great interest from the point of view of the valency of nitrogen. The earlier ideas of the supporters of the theory of constant valency were that nitrogen is always trivalent and that the quaternary derivatives must be considered as 'molecular compounds'. This view had to be abandoned when it was found that the same substance was obtained from trimethylamine and ethyl iodide as from ethyldimethylamine and methyl iodide. The valency of the nitrogen in these compounds was clearly five. It became increasingly evident that the mode of attachment of all the five groups is not the same; the ammonium salts are ionized compounds, and while the four methyl groups remain attached to the nitrogen atom when tetramethylammonium chloride is dissolved in water, the chlorine leads an independent existence as a chloride ion. Werner expressed this clearly in his *Lehrbuch der Stereochemie* (1904, p. 310) by writing ammonium chloride as

$$\left[\begin{matrix} H \\ H \end{matrix} \!\! > \! N \! < \!\! \begin{matrix} H \\ H \end{matrix} \right] Cl,$$
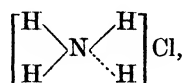
and he subsequently abandoned the distinction between the dotted and full lines and recognized that all the hydrogen atoms are similarly attached. The distinction between the ionized valency and the non-ionized valencies was very apparent when J. Meisenheimer showed that $[Me_3N \cdot OMe]OH$ and $[Me_3N \cdot OH]OMe$ were not identical compounds[1] (see p. 169). Fuller understanding of the problem was reached with the development of the electronic theory of valency by G. N. Lewis and W. Kossel and with the recognition of the distinction between covalency and electrovalency. Nitrogen in ammonia has a complete octet of valency electrons, of which six are shared. If it were to unite with a fourth (neutral) hydrogen atom, there would be nine electrons, so that one is expelled leaving an NH_4 group with a positive charge. Alternatively, the formation of the ammonium ion can be regarded as the union of the ammonia molecule with a proton

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[1] *Annalen*, 1913, **397**, 273.

by means of the unshared pair of valency electrons of the nitrogen atom in ammonia.

$$H \overset{\times\ \times}{\underset{\times\ \times}{\times\ N\ \times}} + H^+ \longrightarrow \left[H \overset{\times\times}{\underset{\times\times}{\times\ N\ \times}} H \right]^+$$
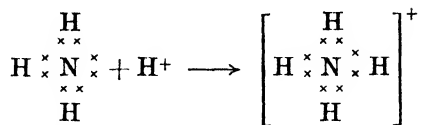
The ion cannot, of course, be isolated except with its anion. This view of the constitution of the ammonium salts is amply confirmed by the behaviour of the compounds containing five hydrocarbon radicals attached to nitrogen which are discussed below (p. 32).

While it is thus evident that in the ammonium salts four of the groups are attached by covalencies and the fifth by an electrovalency, the structure of the substituted ammonium hydroxides is more complex. This raises the question of the strengths of the aliphatic amines as bases, since these strengths are measured by the extent of ionic dissociation of the hydroxides. The quaternary hydroxides are strong electrolytes, completely dissociated in all except the most concentrated solutions, and the conception of a dissociation constant cannot be applied to them. All other classes of amines, however, are weak electrolytes, and measurement of their molecular conductivities at a series of dilutions together with a knowledge of the mobilities of their kations, which can be obtained from the conductivities of their salts, leads to an apparent dissociation constant for each amine. This is not the true dissociation constant. If an amine R_3N in water forms a hydroxide which is only partially dissociated into ions, we have the equilibria

$$R_3N + H_2O \rightleftharpoons R_3NHOH \rightleftharpoons R_3NH^+ + OH^-.$$

If in an approximate treatment we assume that activities can be taken as equal to concentrations, we have two relationships governing the equilibria:

$$\frac{[R_3N]}{[R_3NHOH]} = b \quad \text{and} \quad \frac{[R_3NH^+][OH^-]}{[R_3NHOH]} = K.$$

K is the true dissociation constant of the quaternary hydroxide and a measure of its strength as a base. The apparent dissociation constant K_1 which is obtained by neglecting the distinction between the free amine and the quaternary hydroxide will be given by

$$K_1 = \frac{[R_3NH^+][OH^-]}{[R_3N]+[R_3NHOH]} = \frac{K[R_3NHOH]}{[R_3N]+[R_3NHOH]} = K \times \frac{1}{b+1}.$$

Thus the true dissociation constant will be bigger than the apparent, but to what extent is unknown until the magnitude of b has been obtained. No one measurement can give the required information, but T. S. Moore[1] showed that by measuring at three temperatures the apparent dissociation constant, and also the partition-coefficient of the amine between water and some immiscible solvent, and making the assumption that the temperature coefficients of these quantities are constant over the small temperature

[1] *J.C.S.* 1907, **91**, 1373, 1379; Moore and T. F. Winmill, ibid. 1912, **101**, 1635.

range involved, sufficient equations can be obtained to solve the problem. The results at 25° are shown below; K is the true dissociation constant and the hydration constant is $[R_3NHOH]/[R_3N]$ ($= 1/b$).

	$K \times 10^7$	Hydration constant
Ammonia . . .	0·341	1·13
Methylamine . . .	5·04	15·3
Ethylamine . . .	7·44	2·31
Propylamine . . .	4·77	10·5
Dimethylamine . .	20·32	0·46
Diethylamine . . .	11·36	Large
Dipropylamine . .	9·49	Large
Trimethylamine . .	1·01	1·80
Triethylamine . .	11·26	1·10

These results disclose two important facts. The first is that introduction of alkyl groups into ammonia increases the true basic strength, but only to a comparatively small extent, and the hydroxides derived from primary, secondary, and tertiary alkylamines are all quite weak bases. The increase follows no simple rule and must be governed by a number of factors. The second fact is that all these amines exist in aqueous solution to a considerable extent as undissociated hydroxides. We are thus faced with the problem of finding a structure for these hydroxides; the structure $[R_3NH]OH$, similar to that of the quaternary hydroxides $[R_4N]OH$, is clearly impossible because it implies a strong electrolyte, and not a very weak base.

The key to this problem lies in the enormous increase in basicity which occurs when we pass from a tertiary to a quaternary hydroxide. Undissociated hydroxides are only found when there is at least one hydrogen atom attached to nitrogen, and this hydrogen atom must be involved in the non-ionized linkage which holds the molecule together. Two possibilities present themselves: we can regard the molecule as made up of an ammonium ion and a hydroxyl ion united by a hydrogen-bond,

$$\overset{+}{R_3N}-H\cdots\overset{-}{O}-H,$$
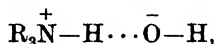
or the hydroxide can be considered as formed from the amine and a water molecule, a hydrogen-bond being formed between a hydrogen atom of the latter by the unshared pair of electrons of the trivalent nitrogen atom,

$$R_3N\cdots H—O—H.$$
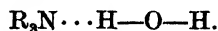
These are only two ways of expressing the same idea; they both represent a linkage between the nitrogen and hydrogen atoms, and this linkage is the essence of the existence of the undissociated hydroxide.[1] The quaternary hydroxide $[R_4N]OH$ cannot assume a structure of this kind, because it contains no hydrogen atom which can take part in hydrogen-bond formation. A parallel difference is that between the alcohols, ROH, and the ethers,

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[1] See W. M. Latimer and W. H. Rodebush, *J. Amer. C. S.* 1920, **42**, 1419.

ROR: the former are associated liquids and the latter are not, because the alcohols contain a hydrogen atom which can form a hydrogen-bond with the oxygen atom of another molecule, while the ethers do not. These considerations find full confirmation in the basicity of the amine oxides, which is discussed later (p. 167). The nature of the link to hydrogen which is involved in all these three classes of compounds is discussed in the Introduction.

The existence of the undissociated hydroxides of the simple aliphatic amines also manifests itself in the remarkable effect of temperature on the solubility of certain amines in water. If a liquid is not completely miscible with water, in the large majority of cases a rise of temperature increases the mutual solubilities of the two liquid layers, until the critical solution temperature is reached at which they become completely miscible. For certain amines, however, such as triethylamine, these relations are reversed; at low temperatures they are completely miscible with water but on warming they become partially miscible and two layers are formed. Further increase of temperature at first decreases the mutual solubilities and then later increases them. Nicotine is the extreme case; below 60° and above 210° it is soluble in water in all proportions, but between these temperatures it is only partially miscible. The peculiar phenomenon of a decrease in solubility with rise of temperature must be due to a change in the nature of the solute with temperature, the solute changing with rise of temperature into a much less soluble substance. An amine can exist in solution as the hydrate R_3NHOH, which, being hydroxylic, is presumably readily soluble in water, and also as the unhydrated amine R_3N. The solubility of both these substances will increase with rise of temperature, but their proportion will also change. Moore found that triethylamine is 70 per cent. hydrated at 15°, but less than 50 per cent. at 32·5°. Hence the effect of raising the temperature is to increase the proportion of the less soluble form, and this must overcome the normal increase of solubility with temperature and cause the total solubility to diminish. At higher temperatures, where practically none of the base is hydrated, it is really the solubility of the anhydrous base that is being measured and this will increase with temperature and may, as with nicotine, give an upper critical solution temperature.

Derivatives containing Five Hydrocarbon Radicals attached to Nitrogen

Very few compounds of this class are known, but their exceptional behaviour is one of the clearest indications that nitrogen cannot form five covalencies. Most attempts to prepare compounds of the type NR_5 have failed,[1] but if sodium benzyl, ϕCH_2Na, or sodium triphenylmethyl, ϕ_3CNa, in ethereal solution is treated with tetramethylammonium chloride, with exclusion of all oxygen, tetramethylammonium benzyl, $Me_4NCH_2\phi$,

[1] H. Staudinger and J. Meyer, *Helv. Chim. Acta*, 1919, **2**, 608.

and tetramethylammonium triphenylmethyl, $Me_4NC\phi_3$, can be obtained. They are bright-red solids, which immediately char in air and react with water to give the quaternary ammonium hydroxide and a hydrocarbon, and with carbon dioxide to give the quaternary ammonium salt of a carboxylic acid:[1]

$$Me_4NCH_2\phi + H_2O \longrightarrow [NMe_4]OH + H_3C\cdot\phi$$
$$Me_4NCH_2\phi + CO_2 \longrightarrow [NMe_4]O_2C\cdot CH_2\phi.$$
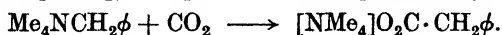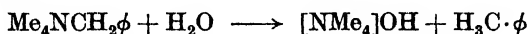
The triphenylmethyl compound gives a conducting solution in pyridine. The compounds are clearly salts and contain an electrovalently linked hydrocarbon anion; their formulae must be written $[NMe_4]CH_2\phi$ and $[NMe_4]C\phi_3$. This is indicated by the fact that the only compounds of the type which have been prepared contain one hydrocarbon radical which is known from other evidence to be able to exist as an anion. This is well shown by the behaviour of the sodium alkyls NaR. These compounds fall into two classes: (1) if R is a simple aliphatic group, the sodium derivative is colourless and insoluble, (2) if R is $C\phi_3$ or $CH_2\phi$, it is red and gives conducting solutions in ether. The pentavalent nitrogen compounds can only be obtained when one of the five groups attached to nitrogen is a radical which forms a sodium derivative of Type 2. If the attempt is made to obtain NMe_5 by the action of sodium methyl on tetramethylammonium iodide, only decomposition products are formed.

The unique behaviour of these compounds affords the strongest evidence that the covalency of nitrogen is limited to four.

The Stereochemistry of Saturated Nitrogen Compounds[2]

Stereochemistry is concerned with the arrangement in space of the atoms which are united to form a molecule. Information on this subject can be obtained from two main sources: (a) the study of stereoisomerism, the type of isomerism which arises from the different arrangement in space of the constituent atoms in a molecule, and is of two kinds, optical and geometrical isomerism; (b) the study of the physical properties of a compound, such as the band-spectrum, the electric moment and diffraction of X-rays and electrons, which depend on the space arrangement of the molecule.

The 'pentavalent' compounds of nitrogen such as the quaternary ammonium salts will be dealt with first. Wislicenus in 1877 suggested that van't Hoff's theory of stereoisomerism in carbon compounds might be extended to this group of compounds, and since that date sufficient examples of stereoisomerism have been investigated to establish the configuration of the quaternary ammonium ion beyond reasonable doubt. The four groups covalently linked to nitrogen are arranged tetrahedrally round the nitrogen atom, just as are the four groups attached to the carbon

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[1] W. Schlenk and J. Holtz, *Ber.* 1916, **49**, 603; 1917, **50**, 274.

[2] A detailed account of this subject will be found in the article by Meisenheimer and Theilacker in *Stereochemie*, ed. Freudenberg; Leipzig, 1933, p. 1125.

atom in a compound of tetravalent carbon. The question of the position of the fifth electrovalently linked group, such as the bromide ion in an ammonium bromide, is quite different and is mentioned later. The main facts upon which this conclusion is based are as follows:

(i) A compound of the type [RR'R''R'''N]Br does not exist in geometrically isomeric forms. At one time it seemed probable that if such a compound were synthesized by different routes, the groups attached to nitrogen being introduced in a different order, isomeric compounds were formed. This possibility was later eliminated conclusively.[1] Hence the arrangement of the groups about the nitrogen atom must be sufficiently symmetrical to exclude geometrical isomerism; it is, for example, improbable that the four groups lie in one plane with the nitrogen atom, because geometrical isomers might then exist.

$$\begin{array}{ccc} R & & R' \\ & >N< & \\ R'' & & R''' \end{array} \qquad \begin{array}{ccc} R & & R' \\ & >N< & \\ R''' & & R'' \end{array}$$
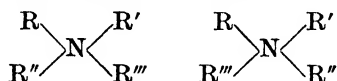
(ii) A compound of the type [RR'R''R'''N]Br can be resolved into optical antimers. The first resolution of a compound of this type was by W. J. Pope and S. J. Peachey;[2] they found that the methyl-allyl-phenyl-benzylammonium salt of d-camphor sulphonic acid could be separated by fractional crystallization from a mixture of acetone and ethyl acetate into two fractions. The iodide derived from the less soluble fraction was dextro-rotatory in solution and that from the more soluble fraction laevo-rotatory. Since 1899 more than twenty compounds of this type have been resolved.

(iii) A compound of the type RR'R''N→O can be resolved into optical antimers. These compounds, called amine oxides, are obtained by the oxidation of tertiary amines (see p. 166). They are monacidic bases and form salts of the type $[R_3N \cdot OH]^+X^-$. The free bases exist in aqueous solution as the hydrates $R_3NOH \cdot OH$ (see p. 168), but can be obtained in the anhydrous state, when their formula is R_3NO. In 1908 J. Meisenheimer resolved methylethyl-aniline oxide, φEtMeNO, by means of d-bromo-camphor sulphonic acid;[3] he found that not only was its chloride,

[φEtMeNOH]Cl,

optically active, which is to be expected since it is of the type discussed in the previous paragraph, but the optical activity is retained by the free base both in aqueous solution when it is hydrated and as the anhydrous oxide in benzene solution.[4] Other amine oxides containing three different hydrocarbon radicals have since been resolved.[5]

[1] E. Wedekind, *Ber.* 1906, **39**, 481; H. O. Jones, *J.C.S.* 1905, **87**, 1721.

[2] Ibid. 1899, **75**, 1127.

[3] *Ber.* 1908, **41**, 3966.

[4] J. Meisenheimer, M. Hoffheinz, and J. Dodonow, *Annalen*, 1911, **385**, 117.

[5] J. Meisenheimer, H. Glawe, H. Greeske, A. Schoring, and E. Vieweg, ibid. 1926, **449**, 188; J. Dodonow, *J. pr. Chem.* 1927, **117**, 154.

In the years that immediately followed the first resolution of a quaternary ammonium salt no great distinction was made between the electrovalently linked anion and the four covalently linked groups in such a compound. The ordinary view was that just as the simplest type of active carbon compounds are those with four different groups attached to one carbon atom, so here there must be five different groups attached to nitrogen. Various models were proposed to represent the arrangement of the five groups; the most commonly accepted was the square-based pyramid of C. A. Bischoff. All these models were unsatisfactory because they imply more than the experimental data justify; even if the anion is always allotted the apex of the pyramid, Bischoff's model suggests that a compound, $[Na_2b_2]X$, should exist in the two geometrically isomeric forms, which are shown in the diagram below, and these have never been obtained.
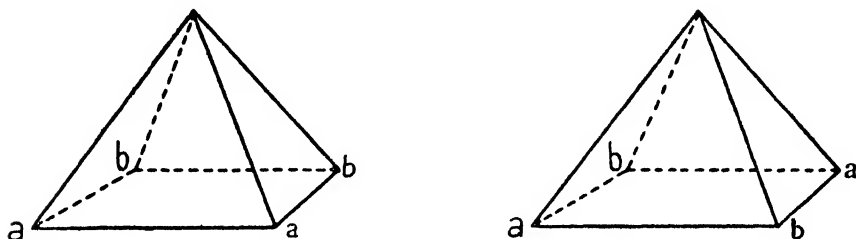
From other points of view as well such models do not represent the facts. The asymmetric quaternary salts are active in dissociating solvents and they are strong electrolytes; it seems hardly likely that the enantiomorphism arises from the arrangement of five groups about the nitrogen atom, since in such solvents one of the five is not there at all.

The resolution of the amine oxides in their unhydrated form shows that the enantiomorphism arises from the arrangement of four groups about the nitrogen atom, and Meisenheimer put forward the view that these four groups are arranged in a tetrahedral fashion, just as are the groups attached to a carbon atom. The fact that the hydrated oxides are optically active, although they must contain two hydroxyl groups, while repeated attempts to resolve compounds such as $[Me_2N\phi \cdot Pr]Br$ have always failed, is a striking stereochemical confirmation of the distinction between electrovalency and covalency in the compounds of pentavalent nitrogen. The resolution of the amine oxides establishes a further point. The bond between oxygen and nitrogen in the unhydrated oxide behaves for stereochemical purposes like the single links that hold the groups in a quaternary ion; it is unlike the double bond of a carbonyl group $>C=O$. If nitrogen cannot show a covalency of five, the reason for this fact is clear. A true double bond between oxygen and nitrogen would involve two electrons from each atom to form a four-electron bond, and this must mean a ten-electron shell about the nitrogen atom. The actual bond is formed by two electrons, the unshared pair of the nitrogen atom, so that there is no

increase in the number of electrons round the nitrogen atom when the bond is formed. The link (a co-ordinate link or semi-polar double bond) does not differ from a single link except in the origin of the electrons which form it and the resulting unsymmetrical distribution of electric charge; hence stereochemically it is indistinguishable from an ordinary single link.
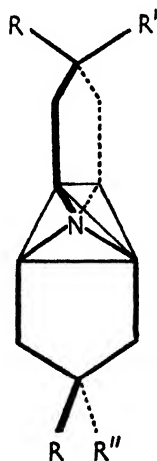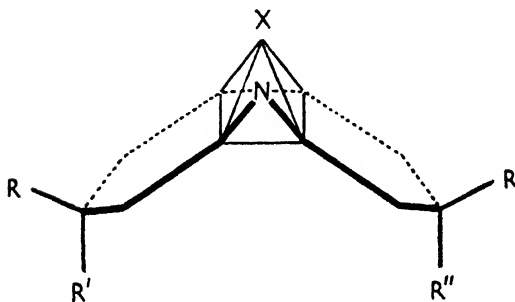
The tetrahedral arrangement of the four groups covalently attached to nitrogen is confirmed by several other experimental facts. van't Hoff pointed out that one consequence of the tetrahedral arrangement about a carbon atom is that compounds of the types

$$\begin{array}{ccc} \underset{b}{\overset{a}{>}}C{:}C{:}C\underset{b}{\overset{a}{<}} & \underset{b}{\overset{a}{>}}C{:}C{:}C\underset{c}{\overset{a}{<}} & \underset{b}{\overset{a}{>}}C{:}C{:}C\underset{d}{\overset{c}{<}} \end{array}$$
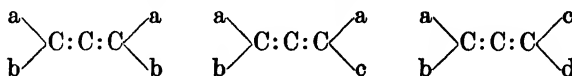
should be capable of resolution, and the same must be true if one or both of the double bonds are replaced by a saturated ring. This has been amply confirmed in the carbon compounds.[1] If the nitrogen arrangement is tetrahedral, optical activity should be found when one of the carbon atoms in these types is replaced by a pentavalent nitrogen atom W. H. Mills and E. H. Warren[2] prepared 4-phenyl-4'-carbethoxy-bispiperidinium-1,1'-spirane bromide

$$\underset{H}{\overset{\phi}{>}}C\underset{CH_2-CH_2}{\overset{CH_2-CH_2}{<}}\overset{+}{N}\underset{CH_2-CH_2}{\overset{CH_2-CH_2}{<}}C\underset{H}{\overset{CO_2Et}{<}} \quad [Br]^-$$
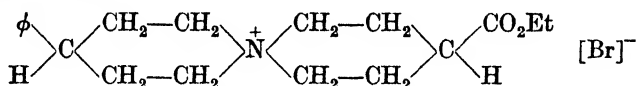
and found it could be resolved by the usual means. Their argument is particularly ingenious because if Bischoff's pyramidal model is true, this molecule has a plane of symmetry and resolution would be impossible. This is shown in the diagrams, in which thin lines represent lines lying in the plane of the page, thick lines those above it and dotted lines those below it.

[1] W. H. Perkin, W. J. Pope, and O. Wallach, *J.C.S.* 1909, **95**, 1793: E. P. Kohler, J. T. Walker, and M. Tishler, *J. Amer. C. S.* 1935, **57**, 1743: P. Maitland and W. H. Mills, *J.C.S.* 1936, 987.   [2] Ibid. 1925, **127**, 2507.

Another confirmation of the tetrahedral arrangement about a carbon atom is the existence of geometrical isomers in saturated cyclic systems, which has been recognized for many years; a well-known example is the *cis* and *trans* forms of the cyclohexane dicarboxylic acids. Analogous geometrical isomerism should appear in suitable nitrogen compounds. W. H. Mills, J. D. Parkin, and W. J. V. Ward[1] studied the quaternary salts formed from 4-phenyl-1-alkylpiperidines and the corresponding 4-hydroxy compounds by the action of alkyl halides.
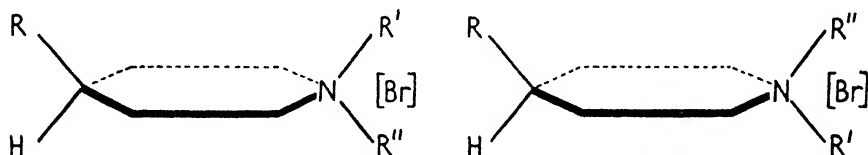
R = ϕ or OH; R' and R" are alkyl groups.

In every case where R' and R" were different alkyl groups the product was a mixture of two isomers, which could be separated because of their different solubilities, while if R' and R" were the same, only one substance was formed. The differences in the properties of the isomers are similar to those between the geometrical isomers in the carbon compounds.

The final confirmation comes from the X-ray determination of the crystal structure of tetramethyl and tetraethyl ammonium halides.[2] The crystals of these substances are similar to those of other salts, in that they consist of a space pattern of independent kations and anions; they are not patterns whose units are complete molecules and it is impossible by inspection of the structure to allot one particular anion to one kation. The crystal structure of tetramethylammonium chloride is derived from that of ammonium chloride by a distortion which results from the larger volume occupied by the tetramethylammonium ion. Each nitrogen atom has a tetrahedral arrangement of four methyl groups about it. These results give powerful support to the distinction between the electro-valently linked anion and the four covalently linked groups which has been emphasized above. The anion has no particular position with respect to one nitrogen atom in the solid state; in solution it leads an independent existence for the greater part of the time. Association of ions undoubtedly takes place in solution, but there is no evidence to show whether in associated ion-pairs the anion and kation assume a certain preferred position or not.

The racemization of optically active quaternary ammonium salts is a complicated subject which cannot be discussed in detail. The sulphates, nitrates, and fluorides are difficult to racemize, while the other halides, especially the iodides, racemize more readily. The rate of racemization is smallest in water and greatest in chloroform. The racemization arises from

[1] *J.C.S.* 1927, 2613.   [2] R. W. G. Wyckoff, *Z. Krist.* 1928, **67**, 91, 550.

the setting up of an equilibrium between the salt and its dissociation products, the tertiary amine and alkyl halide:[1]

$$[NR_4]I \rightleftharpoons NR_3 + RI.$$
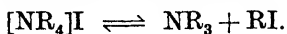
The tertiary amine is never optically active, so that eventually the total activity disappears. This mechanism gives a reasonable explanation of the influence of the nature of the anion and solvent.

The salt of any tertiary amine which contains three different groups united to nitrogen might be expected to exist in optically active forms, because it contains the asymmetric kation $[NHRR'R'']^+$. No such case is, however, known; the salt formed from such an amine and bromocamphor sulphonic acid remains completely homogeneous on recrystallization. This is most probably due to extremely ready racemization taking place by a process similar to that above, dissociation to the free tertiary amine. This may well take place extremely readily by the kation losing a proton to a molecule of solvent and being converted into the tertiary amine. J. Meisenheimer has, however, found[2] one example, a coordination compound of cobalt, in which a quaternary nitrogen atom with one hydrogen atom attached behaves as a centre of asymmetry.

The arrangement of the three groups attached to a trivalent nitrogen atom, as in an amine Nabc, was for long one of the outstanding problems of stereochemistry. The two alternatives are (a) that the nitrogen atom lies in one plane with the three attached groups, so that the whole molecule has a plane of symmetry; (b) that it does not lie in that plane, so that the molecule is pyramidal in shape. The latter alternative is suggested by two independent lines of evidence. The first is that in compounds of the type abC=Nc, such as the oximes, geometrical isomerism has been established beyond doubt (see p. 175). If the three valencies of nitrogen lie all in one plane, the doubly linked compound would be expected to have a symmetrical structure (I), while it quite clearly has an unsymmetrical structure (II).
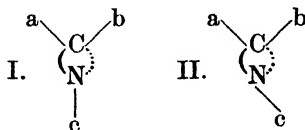
Again it is possible to argue by analogy with the neighbouring elements in the Periodic Table. We should expect an element when ionized to be analogous stereochemically with its predecessor in the Table. A carbon atom, for example, possesses four valency electrons and a nitrogen atom five; if the nitrogen atom loses one electron, that is, becomes a kation, it would seem probable that the remaining four will give rise to bonds with the same space arrangement as those of a carbon atom. There is ample evidence of this in the similarity between the stereochemistry of carbon and pentavalent nitrogen which has been discussed above. Thus the

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[1] H. v. Halban, *Ber.* 1908, **41**, 2417; E. Wedekind and F. Paschke, *ibid.* 2659.
[2] *Annalen*, 1924, **438**, 217.

stereochemistry of un-ionized trivalent nitrogen should resemble that of positively charged oxygen. Little is known of this, but because elements which belong to the same group in the short periods of the Table (e.g. carbon and silicon, nitrogen and phosphorus) resemble one another stereochemically, the argument can be extended to the sulphonium salts. Now compounds of the type $[Sabc]^+X^-$ have been resolved, so the three covalencies of sulphur cannot lie in one plane, and by analogy those of trivalent nitrogen cannot do so either.

This conclusion is upheld by certain of the physical properties of ammonia. The molecule NH_3 has an electric moment of $1 \cdot 5\,D$;[1] if the three hydrogen atoms lie in one plane with the nitrogen atom, the molecule would have a centre of symmetry and its electric moment should be zero. The absorption spectrum of ammonia in the infra-red affords yet more powerful evidence; the absorption arises from the vibrations of the parts of the molecule with respect to one another and from the rotation of the molecule as a whole, and the observed frequencies at which absorption takes place can be translated into the possible states of vibrational and rotational energy, and these are intimately bound up with the 'shape' of the molecule. R. M. Badger and R. Mecke[2] found that the molecule is pyramidal and the angle between its vertical axis and a line joining a hydrogen atom with the nitrogen atom is 58°; this result means that the angle between the valencies which unite nitrogen and hydrogen is 94·5°. The crystal structure of solid ammonia[3] also indicates a pyramidal molecule.

In spite of this overwhelming evidence the fact remains that the most obvious stereochemical deduction from the non-planar arrangement of the valencies has never been confirmed experimentally. A tertiary amine with three different groups attached to nitrogen must be an enantiomorphous arrangement and such amines should be resolvable into optical antimers.

III.
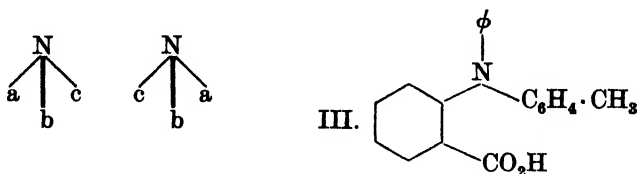
A very large number of attempts have been made to resolve compounds of the most diverse kind which belong to this type, but all have failed. The most noteworthy was, perhaps, that of J. Meisenheimer[4] who prepared the triarylamine (III) in which the nitrogen is non-basic so that no complications are introduced by a change of valency of the nitrogen during

[1] C. J. Zahn, *Phys. Review*, 1926, **27**, 455; H. E. Watson, *Proc. Roy. Soc.* A, 1928, 117, 43.

[2] *Z. phys. Chem.* B, 1929, **5**, 333.

[3] H. Mark and E. Pohland, *Z. Krist.* 1925, **61**, 532; I. de Smedt, *Bull. Acad. roy. Belg.* 1925, **11**, 655.

[4] With L. Augermann, O. Finn, and E. Vieweg, *Ber.* 1924, **57**, 1746.

the resolution. The compound forms easily crystallized salts with several optically active bases, but no resolution could be achieved. The most probable cause of these failures is that the compounds racemize so readily that optical activity cannot persist for any appreciable time. The mechanism of this easy racemization is indicated by the doublet structure of many of the lines in the absorption spectrum of ammonia.[1] This suggests that at ordinary temperatures one of the possible vibrations of the ammonia molecule is that of the nitrogen atom from a position above the plane of the hydrogen atoms to one below. Such an oscillation will mean racemization because an asymmetric molecule is converted into its enantiomorph. In diagram IV is one configuration before the change in position of the nitrogen atom takes place, V is after the change, and VI is V turned upside down and rotated through 180° to show that it is the enantiomorph of IV. In the case of aryl amines such as III, another factor, resonance, will make resolution even less probable. The two free electrons of the nitrogen atom are partially shared with the aromatic nuclei, so that the three valency bonds of the nitrogen atom become partly double bond in character, with the result that the whole molecule must tend to assume a planar structure. The case is stereochemically analogous to that of pararosaniline; three of the planar components of the resonance hybrid are shown on p. 93.

IV.   V.   VI.
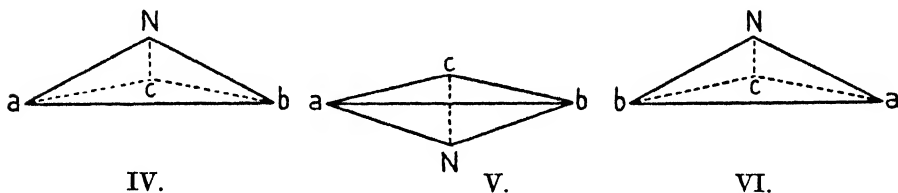
The only point which remains obscure is the absence of a similar racemization in the analogous sulphur compounds such as the sulphonium salts which contain the ion $[Sabc]^+$ and the sulphoxides $abS \rightarrow O$, though in the latter case it is probable that the S–O bond is not a simple co-ordinate link.[3] Both these classes of compounds have been resolved and some show considerable optical stability.

Substituted Alkylamines

Only a few of the many known classes of substituted alkylamines can be described here. N-chloramines, which contain one or two chlorine atoms attached to nitrogen, can be obtained by the action of sodium or calcium hypochlorite on primary and secondary amines:

$$RNH_2 + 2NaOCl \longrightarrow RNCl_2 + 2NaOH$$
$$R_2NH + NaOCl \longrightarrow R_2NCl + NaOH.$$
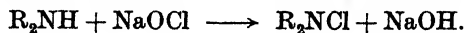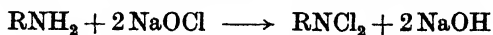
Both monochloramines and dichloramines are also formed by the action of bleaching-powder on tertiary amines, one or two alkyl groups being eliminated as aldehydes. J. Meisenheimer[2] has shown that the course of

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[1] E. F. Barker, *Phys. Review*, 1929, **33**, 684; R. M. Badger, ibid. 1930, **35**, 1038.

[2] *Ber.* 1913, **46**, 1148.

[3] See L. E. Sutton, *Ann. Reports C. S.* 1940, **37**, 73 et seq.

this reaction is first the formation of a quaternary salt containing chlorine in the kation, followed by loss of hydrogen chloride to give an imino compound which is hydrolysed to an aldehyde and an amine; the latter then reacts with the hypochlorite to give the chloramine:
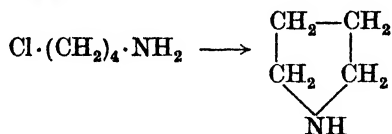
$$Me_3N + Cl_2 \longrightarrow [Me_3NCl]Cl \longrightarrow HCl + [Me_2N:CH_2]Cl$$
$$\longrightarrow CH_2O + Me_2NH.$$
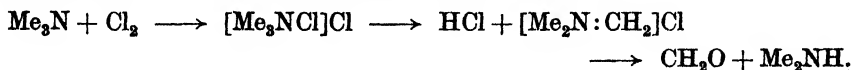
The mono- and dichloramines are unstable oils insoluble in water and are less explosive than nitrogen trichloride; many of them can be distilled. They show the same type of hydrolysis as nitrogen trichloride, being converted by acids into amines and hypochlorous acid, and not into hydroxylamines and hydrogen chloride:

$$R_2NCl + H_2O \longrightarrow R_2NH + HOCl.$$
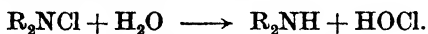
N. V. Sidgwick[1] has suggested that this characteristic reaction of a chlorine atom attached to nitrogen is due to the co-ordination of the hydrogen of the water with the unshared pair of electrons of the nitrogen atom.

$$R-N\begin{array}{c}R\\ \diagdown Cl\\ \downarrow\\ HOH\end{array} \longrightarrow R-N\begin{array}{c}R\\ \diagdown H\end{array} +HOCl$$
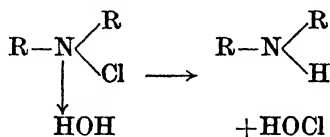
Aliphatic amines with halogen substituents in the alkyl groups can be obtained by obvious modifications of the general methods of preparing amines which have been described. They are stable as their salts, but some of them are converted by alkali into cyclic bases (see p. 468). Thus δ-chloro-n-butylamine gives pyrrolidine.

$$Cl \cdot (CH_2)_4 \cdot NH_2 \longrightarrow \begin{array}{c} CH_2-CH_2 \\ | \quad\quad | \\ CH_2 \quad CH_2 \\ \diagdown \; / \\ NH \end{array}$$

Hydroxy-amines or Amino-alcohols.

The α-hydroxy-amines are the aldehyde-ammonias formed by passing dry ammonia into the ethereal solutions of aldehydes of low molecular weight, or treating them with aqueous ammonia. They have been allotted the general formula $R \cdot CHOH \cdot NH_2$, but their constitution and behaviour is not completely understood. They are crystalline solids which are somewhat unstable and are decomposed by warming with dilute acids into the aldehyde and ammonia; for this reason they are sometimes used for the purification of aldehydes (ketones react with ammonia to give complex condensation products, see triacetonamine, p. 540). The compound derived from acetaldehyde, usually called 'aldehyde-ammonia', has been used as a catalyst in vulcanization. It almost certainly has a constitution which is more complicated than the simple formula $CH_3 \cdot CHOH \cdot NH_2$: molecular weight determinations in solutions give values which are two to three

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[1] *J.C.S.* 1924, **125**, 2672.

times that required by the simple formula.[1] It loses water if kept over sulphuric acid *in vacuo* giving a compound $(C_2H_5N)_n$, which regenerates ordinary aldehyㅗe-ammonia if treated with water.

Formaldehyde behaves differently with ammonia and gives hexamethylenetetramine, $C_6H_{12}N_4$. This is a crystalline compound which can be sublimed unchanged and is stable in alkaline solution but is hydrolysed by acids mainly to formaldehyde and ammonia. It is used in medicine as a mild antiseptic. The crystal structure of the compound is known in great detail.[2] The carbon atoms all occupy equivalent positions in the structure and lines joining those positions form a regular octahedron; the four nitrogen atoms are also in equivalent positions and are arranged in a regular tetrahedron; this is shown in the figure, in which the black spheres represent the carbon atoms and the lighter spheres the nitrogen atoms.
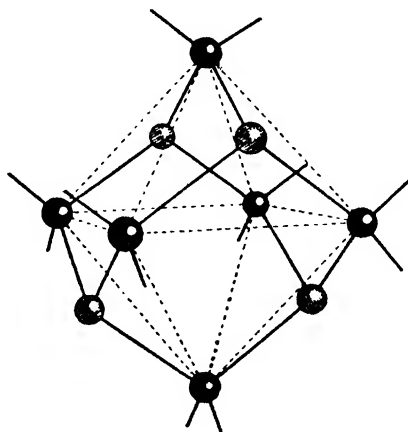
The β-hydroxy-amines are quite different from the aldehyde ammonias. They are mostly alkaline viscous liquids which are soluble in water and show no tendency to lose ammonia. In addition to the obvious methods of preparation, they can be obtained by the action of ammonia on ethylene oxides:

$$CH_2\text{---}CH_2 + NH_3 \longrightarrow HOCH_2 \cdot CH_2 \cdot NH_2.$$
$$\diagdown O \diagup$$

Since the hydroxy-amine can react with a further molecule of the oxide, and the process can be repeated with the product, the reaction gives a mixture of primary, secondary, and tertiary amines, which can be separated by distillation under reduced pressure or by fractional crystallization of their salts. The final product of the action of ethylene oxide itself with ammonia is tri-β-hydroxyethylamine (triethanolamine) $(CH_2OH \cdot CH_2)_3N$; this is prepared commercially and is used as a gas adsorbent and in com-

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[1] O. Aschan, *Ber.* 1915, **48**, 874.

[2] R. G. Dickinson and A. L. Raymond, *J. Amer. C. S.* 1923, **45**, 22; R. W. G. Wyckoff and R. B. Corey, *Z. Krist.* 1934, **89**, 462.

bination with fatty acids as a neutral soap which is an excellent emulsifying agent.[1]

The quaternary hydroxide, $[CH_2OH \cdot CH_2 \cdot NMe_3]OH$, is called choline and is very widely distributed in living organisms; it has been found in almost all plants and in many animal tissues.[2] It is usually known as a viscous, hygroscopic liquid, but has been obtained with difficulty in the crystalline state. Its salts are crystalline; the double chloride of choline and mercury, $[C_5H_{14}ON]Cl,6HgCl_2$, is sparingly soluble and has been used for the identification and separation of the compound. It has been obtained synthetically by various methods: an example is the action of aqueous trimethylamine on ethylene oxide:

$$CH_2\!\!-\!\!CH_2 + NMe_3 + H_2O \longrightarrow [CH_2OH \cdot CH_2 \cdot NMe_3]OH.$$
$$\diagdown\!O\!\diagup$$
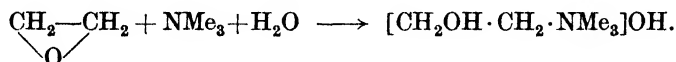
It is stable in dilute aqueous solution, but more concentrated solutions when heated give trimethylamine and ethylene glycol, $CH_2OH \cdot CH_2OH$. It has a marked physiological action, paralysing the motor nerves so that with large doses death follows by the inhibition of respiration. Another β-hydroxy quaternary ammonium compound of high physiological activity is muscarine, the poisonous principle of certain toadstools. This most probably has the structure[3]

$$Et \cdot CHOH \cdot CH \cdot CHO$$
$$|$$
$$NMe_3[OH]$$
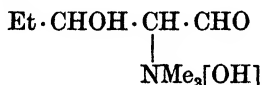
Aliphatic Diamines

Of the aliphatic diamines the best known are those derived from the straight chain hydrocarbons with an amino group on each terminal atom, $H_2N \cdot (CH_2)_n \cdot NH_2$. They are most conveniently obtained by the action of ammonia or phthalimide on the corresponding halogen compounds, or by the reduction of the nitriles of the dicarboxylic acids. They are liquids or low-melting solids, and in the homologous series $H_2N \cdot (CH_2)_n \cdot NH_2$ the melting-points show alternation like those of the dibasic acids.

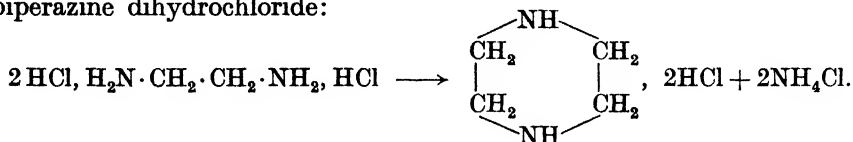| $n =$	2,	3,	4,	5,	6,	7,	8,	9,	10
melting-point =	8·5°,	liquid,	27°,	liquid,	42°,	29°,	51°,	37°,	62°.

They are readily soluble in water and some form hydrates of considerable stability, a behaviour which recalls that of hydrazine. Some of these diamines occur in nature as the products of bacterial decomposition of proteins; their formation takes place by loss of carbon dioxide from the diamino-acids which are protein constituents. Thus putrescine $H_2N(CH_2)_4NH_2$ is formed from ornithine, $H_2N(CH_2)_3 \cdot CHNH_2 \cdot CO_2H$, and

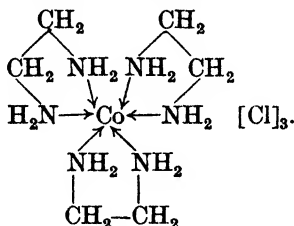[1] See A. L. Wilson, *Ind. Eng. Chem.* 1930, **22**, 143.

[2] See G. Klein, *Handbuch der Pflanzenanalyse*, Vienna 1933, vol. iv/1, p. 275; O. Fürth, *Lehrbuch der physiologische Chemie*, Leipzig, 1928, vol. i, p. 112.

[3] F. Kögl, H. Duisberg, and H. Erxleben, *Annalen*, 1931, **489**, 156.

cadaverine, $H_2N(CH_2)_5NH_2$, from lysine, $H_2N(CH_2)_4 \cdot CHNH_2 \cdot CO_2H$. The hydrochlorides of certain of these diamines are converted on dry distillation with loss of amronium chloride into the salts of cyclic bases. As would be expected from the simple application of strain theory, this takes place very readily when a five- or six-membered ring is formed; thus putrescine dihydrochloride gives pyrrolidine (see p. 492). With ethylene diamine, however, the three-ring is not formed, but two molecules react to give piperazine dihydrochloride:

$$2\,HCl,\ H_2N \cdot CH_2 \cdot CH_2 \cdot NH_2,\ HCl \longrightarrow \begin{array}{c} \text{NH} \\ \text{CH}_2 \quad\quad \text{CH}_2 \\ | \quad\quad\quad | \\ \text{CH}_2 \quad\quad \text{CH}_2 \\ \text{NH} \end{array},\ 2\,HCl + 2\,NH_4Cl.$$

The diamines with amino groups on adjacent carbon atoms, ethylene diamine and its alkyl substitution products, form very stable co-ordination compounds with the metals which belong to or are near to the transitional groups in the Periodic Table. In these complexes both of the nitrogen atoms are united to the metal by a co-ordinate link formed by the unshared pair of electrons of the nitrogen atom. They are thus cyclic compounds with five members in the ring, and the structure of the complex formed from cobaltic chloride with three ethylene diamine molecules, usually written $[\text{Coen}_3]Cl_3$, can be written:

$$\begin{array}{c} \text{CH}_2 \quad\quad\quad \text{CH}_2 \\ \text{CH}_2 \ \ \text{NH}_2 \ \text{NH}_2 \ \ \text{CH}_2 \\ \text{H}_2\text{N} \longrightarrow \text{Co} \longleftarrow \text{NH}_2 \quad [\text{Cl}]_3. \\ \text{NH}_2 \ \ \text{NH}_2 \\ | \quad\quad | \\ \text{CH}_2 \!-\! \text{CH}_2 \end{array}$$

The study of compounds of this type has been of the greatest importance in the development of the stereochemistry of the metals.[1] The simple primary amines such as methylamine unite with metals to form amines much less readily than ammonia itself; from this fact it might have seemed likely that the cyclic amines derived from ethylene diamine would be no more stable than those of the primary amines. Actually, however, the ethylene diamine complexes are extremely readily formed and very stable; this may be due in some unknown way to the ring structure.

Aliphatic amines containing more than two amino groups are known and some of them occur in living organisms. An interesting example is spermine, which is widely distributed in the organs of mammals and is also found in yeast; it can be separated as its phosphate. The compound contains two primary and two secondary amino groups, and synthesis[2] has shown that it is 1,4 bis(aminopropylamino)-n-butane,

$$NH_2 \cdot (CH_2)_3 \cdot NH \cdot (CH_2)_4 \cdot NH \cdot (CH_2)_3 \cdot NH_2.$$

[1] See P. Pfeiffer, *Stereochemie*, ed. Freudenberg, Leipzig, 1933, p. 1268 et seq.
[2] H. W. Dudley, O. Rosenheim, and W. W. Starling, *Biochem. J.* 1926, **20**, 1082.

AROMATIC AMINES

THE primary aromatic amines, properly so called, are those substances in which the amino group is directly attached to an aromatic nucleus, such as that of benzene or naphthalene. They resemble the aliphatic amines in many ways, but there are marked differences in their behaviour towards certain reagents. The majority of these compounds are easily accessible; they are formed by the reduction of the nitro compounds which can be obtained in the aromatic series by direct nitration. In addition they are solids or liquids of high boiling-point and most of their derivatives crystallize well and are easy to handle. Finally they are the starting-point for the preparation of a large number of compounds of great technical importance. Consequently there is scarcely any class of substances which have been investigated with so much industry and so much success.

The basis of our knowledge of aniline and its allies was laid down in 1846–51 by A. W. Hofmann in his 'Contributions to our knowledge of the Volatile Organic Bases'.[1] 'Considering the very modest means at the disposal of the organic chemist, and moreover that he was unable to obtain benzene, much less aniline, as a commercial product, it is astounding the immense number of facts Hofmann discovered which are still among the most important in the whole subject.'[2] Aniline, the simplest of the primary aromatic amines, was first obtained by Unverdorben in 1828 by the distillation of indigo. In 1840 Fritzsche prepared it by distilling indigo with potash and called it aniline from *añil*, the Spanish word for indigo. In 1843 Hofmann showed that this base was identical with that which Runge in 1834 had found in coal-tar, and with that which Zinin[3] had prepared in 1842 by the reduction of nitrobenzene. This last method of preparation proves the formula of the compound. Aniline occurs only in very small quantity in coal-tar, so that this source, which was first adopted, was soon abandoned in favour of the reduction of nitrobenzene.

Methods of Formation of Primary Aromatic Amines

1. *By the reduction of nitro compounds.* This is by far the most general method. The products obtained from nitro compounds by reduction are discussed in a later chapter (p. 252); from that account it will be clear that to obtain the amine almost any acid reducing agent can be used, but weak alkaline and neutral reagents should be avoided. Only the more important of the many methods known will be mentioned. The choice of the reagent depends to a large extent upon the nature of the other groups present in the molecule. If these are unlikely to be attacked, vigorous reagents can

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[1] *Annalen*, 57–79. [2] Meyer and Jacobson, *Lehrbuch*, 1902, ii. 172.
[3] *Annalen*, 44, 286.

be used; in the laboratory, tin and hydrochloric acid or stannous chloride dissolved in hydrochloric acid are often employed, sometimes with the nitro compound in suspension or in alcoholic solution. Zinc and acetic acid are sometimes useful, but zinc and hydrochloric acid, which Hofmann employed, have the disadvantage that by-products containing chlorine are often formed. On the large scale nitrobenzene is reduced to aniline with iron and a small quantity (about $\frac{1}{40}$ of an equivalent) of hydrochloric or sulphuric acid; the ferric salt first formed is largely hydrolysed to ferric hydroxide and the free mineral acid, which reacts again, so that the small quantity of acid acts as a carrier for reduction by the iron and water.

$$\phi \cdot NO_2 + 2Fe + 4H_2O \longrightarrow \phi NH_2 + 2Fe(OH)_3$$
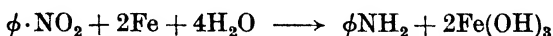
The amine is isolated from the reaction mixture by addition of caustic soda or sodium carbonate (technically lime is used) followed by distillation in steam if it is sufficiently volatile, or extraction with a suitable solvent. Some amines form sparingly soluble double chlorides with stannic chloride, so that with tin or stannous chloride as reducing agent these stanni-chlorides sometimes separate from the reaction mixture; in such cases it is possible to filter off the stannichloride, remove the tin by passing hydrogen sulphide through its aqueous suspension and obtain the amine from the solution after filtering off the stannous sulphide.

A valuable reducing agent for laboratory purposes is titanous chloride ($TiCl_3$) or sulphate dissolved in the corresponding acid. This can be used not only for preparative purposes, but also for the quantitative estimation of nitro groups.

$$R \cdot NO_2 + 6TiCl_3 + 6HCl \longrightarrow R \cdot NH_2 + 6TiCl_4 + 2H_2O$$
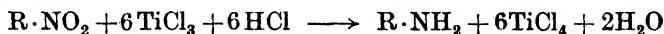
The nitro compound is boiled in an atmosphere of carbon dioxide with a known volume of standard titanous chloride solution and, after cooling, the excess of the latter is back-titrated with a standard solution of ferric alum.[1]

To reduce only one nitro group in a compound that contains several, the usual method is to use the theoretical amount either of sodium disulphide (Na_2S_2) or of sodium hydrosulphide (NaHS), the nitro compound being in alcoholic solution or aqueous suspension:

$$4R \cdot NO_2 + 6NaSH + H_2O \longrightarrow 4R \cdot NH_2 + 3Na_2S_2O_3$$
$$R \cdot NO_2 + Na_2S_2 + H_2O \longrightarrow R \cdot NH_2 + Na_2S_2O_3.$$
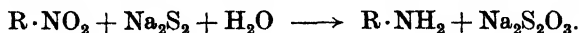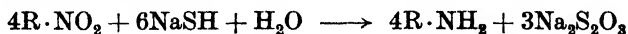
Another way is to add a little ammonia to the alcoholic solution of the nitro compound and then saturate it with hydrogen sulphide; ammonium hydrosulphide is the reducing agent. This was the method used by Zinin in his first reduction of nitrobenzene. A useful feature of this reagent is that it has no action on a nitro group when there is a substituent in the ortho position, so that 2,4-dinitrotoluene is reduced to the 4-amino com-

[1] E. Knecht and E. Hibbert, *New Reduction Methods in Volumetric Analysis*, London, 1925, p. 29.

pound, while other reagents, such as stannous chloride, reduce the 2-nitro group.

$$\text{Me} \quad\overset{\text{(NH}_4)\text{HS}}{\longleftarrow}\quad \text{Me} \quad\overset{\text{SnCl}_2}{\longrightarrow}\quad \text{Me}$$
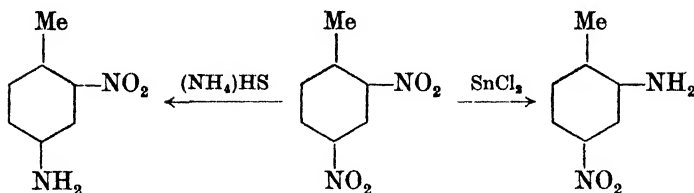
Nitrophenols and nitro-acids are often reduced with ferrous sulphate and ammonia. The nitro compound is dissolved in excess of aqueous ammonia and ferrous sulphate solution added. After heating, the ferric hydroxide is removed and the amino compound precipitated by addition of the correct amount of hydrochloric acid; excess will, of course, dissolve the basic amine. Other reagents suitable for amino phenols are sodium hydrosulphite ($Na_2S_2O_4$), or iron turnings in a solution of calcium chloride. o-Amino-benzaldehyde, a valuable reagent for quinoline syntheses (see p. 547) and an unstable compound, is best obtained by shaking at room temperature a mixture of the nitro-aldehyde and solid sodium carbonate with a solution of ferrous sulphate.[1]

Electrolytic reduction is of little practical value except for the production of amino-phenols. In aqueous hydrochloric or sulphuric acid, the phenylhydroxylamine first formed in the reduction undergoes a 'rearrangement' (see p. 163), so that from nitrobenzene the main product is p-amino-phenol. Similarly, electrolytic reduction of m-dinitrobenzene in concentrated sulphuric acid gives 2,4-diamino-phenol, whose salts are used as developers in photography under the name of 'amidol'.

Nitrobenzene can be reduced catalytically to aniline in very good yield by gaseous hydrogen when certain catalysts are present: of these, finely divided nickel is active at 190°, copper at 250°, and cadmium at 300°.[2] Copper chromite and vanadium are also good catalysts.[3] The nitro group is also attacked in the ordinary laboratory method of catalytic reduction with hydrogen and palladium or platinum at room temperature, but the method is seldom used for the preparation of amines.

2. *Replacement of halogen by* NH_2. In the majority of cases a halogen atom attached to an aromatic nucleus is very unreactive, this being a general property of halogen atoms linked to doubly bound carbon atoms, as in vinyl chloride, $CH_2\!:\!CHCl$. Hence the formation of an amine by the action of ammonia on a halogen compound takes place with much greater difficulty in the aromatic series than in the aliphatic, and the method is not so widely used for the preparation of amines. Chlorobenzene only reacts with ammonia at high temperatures; aniline can be obtained if the two are passed over nickel at 300° or if chlorobenzene is

[1] *Zent.* 1926, i, 230: D.R.-P. 418497.

[2] O. W. Brown and C. C. Henke, *J. Phys. Chem.* 1922, **26**, 161; R. J. Hartmann and O. W. Brown, ibid. 1930, **34**, 2651.

[3] H. A. Doyal and O. W. Brown, ibid. 1932, **36**, 1549.

heated with the calcium chloride-ammonia complex to 350°. The reaction is catalysed to a marked degree by finely divided copper (copper-bronze) or the salts of copper; thus p-phenylene-diamine can be made from p-dichlorobenzene by heating with aqueous ammonia and a little copper sulphate at 170–180°.[1] The reaction can be carried out by passing the vapour of the halogen compound over copper chloride or copper oxide heated to 250°.[2] The method is seldom used in the laboratory for the preparation of simple amines.

A halogen atom attached to an aromatic nucleus is much more reactive if one or more nitro groups are present in the ortho or para positions, and such halogen compounds react readily with ammonia to give primary aromatic amines, and with amines to give secondary and tertiary amines. The extreme case is picryl chloride (2,4,6-trinitrochlorobenzene) which resembles an acid chloride and reacts very readily with ammonia to give picramide. In cases such as these the replacement method has frequently been used for the laboratory preparation of amines.

3. *Replacement of the hydroxyl group by* NH_2. In the benzene series this reaction is of little importance. In the naphthalene series, however, the reaction is frequently used, particularly in the preparation of dye-stuff intermediates. α-Naphthylamine can be obtained by reduction of the α-nitro compound which is formed in the direct nitration of naphthalene, but β-nitronaphthalene cannot be prepared by such simple means. On the other hand, sulphonation of naphthalene at a high temperature gives β-naphthalene sulphonic acid which can be converted into β-naphthol, and it is by replacement of the hydroxyl group by NH_2 that β-naphthyl-amine and its homologues are prepared. This can be effected by heating with the zinc chloride-ammonia complex, but a more important method is that due to H. T. Bucherer.[3] This consists in treating the naphthol under pressure with a solution containing ammonium sulphite and ammonia at 150–180°, when an almost quantitative conversion to the naphthylamine occurs. The reaction seems to take place through the formation of a bisulphite compound of the naphthol which reacts with the ammonia and then loses sulphurous acid.[4]
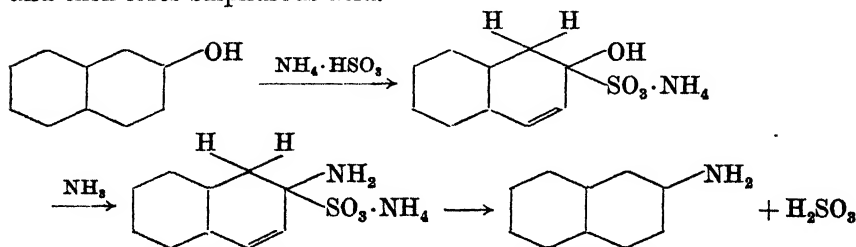
The reverse reaction, the conversion of a naphthylamine into a naphthol, takes place in aqueous sodium bisulphite solution and is used technically in the case of α-naphthylamine sulphonic acids.

[1] *Zent.* 1908, ii, 1221, D.R.-P. 202170.   [2] Ibid. 1932, ii, 1237; Eng. Pat. 370774.
[3] See a series of papers, *J. pr. Chem.* 1904–8.   [4] F. Raschig, *Ber.* 1926, **59**, 865.

4. *Miscellaneous methods.* Some of the methods used in the preparation of aliphatic amines are applicable in the aromatic series. Aromatic acids can be converted into amines by the Curtius degradation of their azides (p. 375) or by the Hofmann degradation of their amides (p. 146). A commercial application of the latter reaction is the preparation from phthalimide of anthranilic acid, which formerly was a stage in the production of indigo (p. 509).
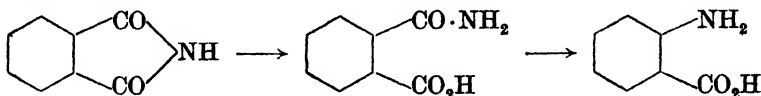
The conversion of an aromatic acid into an amine can also be effected in one stage by hydrazoic acid and concentrated sulphuric acid (see p. 370). The Beckmann rearrangement of the oxime of a phenyl ketone can be used for preparing an aromatic amine, if, as is usually the case, the configuration of the oxime is suitable; thus, acetophenone oxime gives acetanilide which can be hydrolysed to aniline:

$$\phi \cdot C(:NOH) \cdot Me \longrightarrow \phi \cdot NH \cdot COMe \longrightarrow \phi NH_2.$$
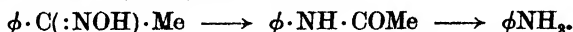
In a few cases the amino group can be introduced by direct substitution of a hydrogen atom attached to the aromatic nucleus. Hydroxylamine and sodium ethoxide condense with certain nitro compounds, notably *m*-dinitrobenzene, 1,3,5-trinitrobenzene, and the nitronaphthalenes to give the sodium salts of complexes which contain one molecule of hydroxylamine to each nitro group. These are decomposed by acids into their original components, but, if left to stand in the cold, they change into amino compounds: thus 2-nitronaphthalene gives 2-nitro-1-naphthylamine. With *m*-dinitrobenzene, two amino groups are introduced and 2,6-dinitro-1,3-phenylenediamine is formed.[1] Sodamide can be used for the direct introduction of an amino group (compare p. 529). α-Naphthol and α-naphthylamine when fused with sodamide give 5-amino-1-naphthol and 1,5-naphthylenediamine respectively.[2]

Properties of the Aromatic monamines

The melting- and boiling-points of some simple amines are as follows:

	m.p.	b.p.
Aniline	−6·24°	184·4°
o-Toluidine, 2-methylaniline	−16·25 (polymorph −24·4)	200·7
m-Toluidine, 3-methylaniline . . .	..	199
p-Toluidine, 4-methylaniline . . .	+45·7	200
vic-o-Xylidine, 2,3-dimethylaniline . .	..	223
asymm-o-Xylidine, 3,4-dimethylaniline . .	51	226
vic-m-Xylidine, 2,6-dimethylaniline . .	..	216
asymm-m-Xylidine, 2,4-dimethylaniline . .	..	215
p-Xylidine, 2,5-dimethylaniline . .	15·5	215
α-Naphthylamine	49	301
β-Naphthylamine	112	·306

[1] J. Meisenheimer and E. Patzig, *Ber.* 1906, **39**, 2533.
[2] F. Sachs, ibid. 1906, **39**, 3006.

Aniline, when pure, is a colourless oil with a bluish fluorescence, but like the majority of liquid aromatic bases it turns brown on exposure to light and air, and technical aniline is a brown liquid. The brown colour is largely removed by distillation. If all traces of impurity, particularly sulphur compounds, are removed, the brown colour is formed very much more slowly; this can be achieved by heating with acetone[1] or by treatment with stannous chloride.[2] At 25° water dissolves 3·7 per cent. of aniline and aniline 5·3 per cent. of water; it is easily soluble in aqueous solutions of its hydrochloride.[3] It is best dried with potassium hydroxide or carbonate; metallic sodium cannot be used because it reacts with aniline. The aromatic amines are much weaker as bases than the aliphatic amines. Aniline is neutral to litmus; the true dissociation constant of the base $\phi \cdot NH_3OH$ is not known, but the apparent dissociation constant (see p. 30) is of the order of 4×10^{-10} at 25°.[4] The salts of aromatic amines are usually well crystallized solids soluble in water, the sulphates usually much less so than the halides. The salts with weak acids are largely hydrolysed in water; aniline acetate is hydrolysed to an extent of 56 per cent. at 25°, the degree of hydrolysis being independent of the concentration, as theory requires, from N/20 to N/500.[5] It is curious that no solid compound of aniline and acetic acid corresponding to the normal salt, $\phi NH_2, CH_3CO_2H$, is known, but only a stable solid, $\phi NH_2, 2CH_3CO_2H$ (m.p. 16·7°), and a meta-stable solid, $2\phi \cdot NH_2, CH_3 \cdot CO_2H$ (m.p. −19·4°).[6] Aniline and its homologues are poisonous, since they destroy the red corpuscles of the blood by combining with the haemoglobin, and aniline must be handled with great care. Aniline poisoning can arise both from prolonged exposure to its vapour and from contact of the skin with the liquid, and if it is spilt on the hands, it should be carefully washed off with dilute acetic acid.

Many of the chemical properties of the aromatic primary amines resemble those of the corresponding aliphatic compounds. Thus a hydrogen atom of the amino group can be replaced by an alkali metal and by alkyl, aryl, and acyl groups. They give isocyanides with chloroform and alcoholic potash (p. 317) and, like hydroxylic compounds, they decompose Grignard reagents.

$$\phi \cdot NH_2 + RMgI \longrightarrow \phi \cdot NH \cdot MgI + RH$$
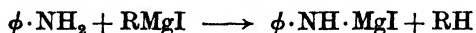
If methyl magnesium iodide is used, methane is evolved and the volume of methane can be used for the estimation of amino groups.[7]

One of the most characteristic differences between the aromatic and the aliphatic primary amines lies in their behaviour towards nitrous acid.

[1] A. Hantzsch and H. Freese, *Ber.* 1894, **27**, 2531, 2996.

[2] A. Weissberger and E. Strasser, *J. pr. Chem.* 1932, **135**, 209.

[3] N. V. Sidgwick, P. Pickford, and B. H. Wilsdon, *J.C.S.* 1911, **99**, 1122.

[4] H. T. Tizard, ibid. 1910, **97**, 2494.

[5] H. T. Tizard, ibid. 2490.

[6] E. A. O'Connor, ibid. 1921, **119**, 400.

[7] J. J. Sudborough and H. Hibbert, ibid. 1909, **95**, 477.

The behaviour of the aliphatic compounds has been discussed above (p. 23): in the great majority of cases, nitrogen is evolved and a hydroxylic compound formed. The aromatic primary amines are converted by nitrous acid into diazo compounds which are basic and give diazonium salts with acids.

$$Ar \cdot NH_2 + ONOH \longrightarrow [ArN_2]Cl$$
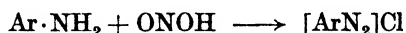
The diazo compounds are of the greatest interest, both practical and theoretical, and are discussed in detail later (Chapter XIII): they are capable of more varied types of reaction than almost any other class of compounds, and the problem of their structure has given rise to a series of investigations which have been of great importance in the history of organic chemistry. The diazo compounds couple with phenols to give hydroxy-azo compounds (see p. 438), which are coloured substances and some of which are used as dye-stuffs. This reaction is often used as a simple laboratory test for a primary aromatic amine; a small quantity of the base dissolved in dilute hydrochloric acid is treated with a few drops of aqueous sodium nitrite and after a few seconds the resulting solution is poured into excess of an alkaline solution of β-naphthol. If the base is a primary aromatic amine, it is converted by the nitrous acid into the diazo compound which couples with the naphthol in alkaline solution to the azo-β-naphthol derivative. This, being an ortho-hydroxy compound, is insoluble in alkali (see p. 440) and separates as an easily recognizable scarlet precipitate.
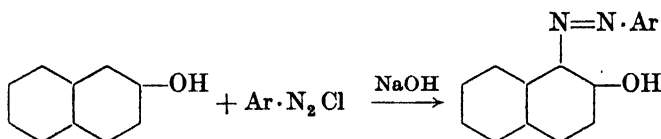
Another reaction in which the primary aromatic and aliphatic amines differ is that with carbon disulphide. Alkylamines react with this compound usually in the cold to give a dithiocarbamic acid which combines with more of the amine to form a salt (see p. 24).
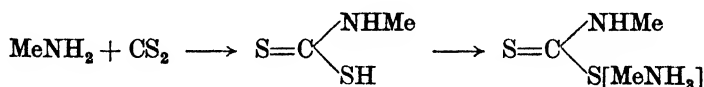
With aromatic amines a similar reaction does not take place unless aqueous ammonia or a metallic hydroxide is added. In those circumstances a salt of a dithiocarbamic acid is formed; otherwise there is no reaction in the cold, but on heating hydrogen sulphide is eliminated and a symmetrical disubstituted thio-urea is formed:
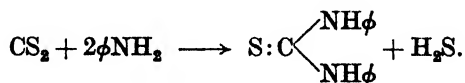
The difference is probably due to the weakness of the aromatic amines as bases compared with the alkylamines.

The oxidation of aniline is a complicated subject; a great variety of

compounds of very different structures can be obtained according to the oxidizing agent used and the conditions of the oxidation. The reaction became of technical importance very soon after the first isolation of aniline and long before the structure of benzene and aniline were properly established, because it gave rise to the first known synthetic dye-stuffs. Owing to this fact an enormous amount of empirical knowledge dealing with the oxidation of aniline was rapidly accumulated, but it was only after many years that the mechanism of the various oxidations was elucidated and the reasons found for the production of such a wide diversity of products. The three primary observations of importance from the technical point of view were:

(a) Runge in 1840[1] found that aniline could be oxidized to insoluble black substances, and immediately made somewhat unsuccessful attempts to use them as dye-stuffs. Great improvements were introduced by Lightfoot (1863) and these led to the general adoption of the compounds as a dye under the name of aniline black. Their constitution is discussed below (p. 56).

(b) In 1856 Sir W. H. Perkin as a youth eighteen years old tried to synthesize quinine by the oxidation of allyltoluidine. Such an attempt seems somewhat strange to-day, but at that time there was little knowledge of organic reactions and none whatever as to the constitution of quinine, apart from its empirical formula. Perkin obtained only a 'dirty reddish brown precipitate', but he continued his experiments and oxidized impure aniline sulphate (containing toluidines) in dilute solution with bichromate. From the resulting resinous mass he isolated a violet dye-stuff which afterwards became known as mauve or mauveine. It was formed in very small yield (5 per cent.) and was the first synthetic dye-stuff to be manufactured.[2] The compound results from a series of successive oxidations and condensations: it is now known to be a phenazine derivative and belongs to the safranine group of dyes; its formula is:
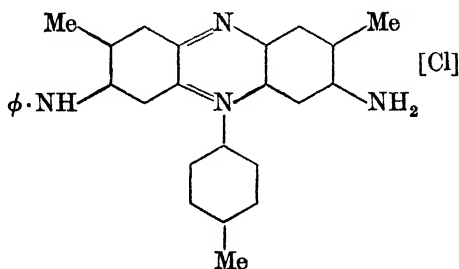
At first it was sold at the extraordinary price of about £20 a pound, but later it was displaced by other synthetic dyes and its manufacture was abandoned. One of its last uses was as colouring matter for the violet British penny postage stamps.

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[1] *J. pr. Chem.* **20**, 464.

[2] See R. Meldola, Obituary notice of Sir W. H. Perkin, *J.C.S.* 1908, **93**, 2214.

(c) Perkin's discovery stimulated many others to investigate the oxidation of aniline, and in 1859 Verguin in France found that by the action of stannic chloride on impure aniline another dye-stuff, magenta or fuchsine, could be obtained. This was the first of the triphenylmethane dyes, which are discussed in detail below (p. 82).

Our knowledge of the mechanism of the oxidation of pure aniline is largely due to the work of E. Bamberger and his pupils (1898–1902) and of Stefan Goldschmidt (1920–4).[1] The many products which can be obtained with different reagents and different conditions can be divided into three groups:

(i) Monomolecular products: e.g. phenylhydroxylamine, ϕNHOH; nitrosobenzene, $\phi \cdot$NO; nitrobenzene, ϕNO$_2$; benzoquinone, O=⟨ ⟩=O.

(ii) Dimolecular products: e.g. azobenzene, ϕN:Nϕ; azoxybenzene, ϕNO:Nϕ; phenyl quinonediimine, HN=⟨ ⟩=Nϕ.

(iii) Polymolecular products. These consist of a large number of compounds some of quite high molecular weight; important examples are emeraldine, nigraniline, and the aniline blacks of which there are two main classes, the so-called 'greenable' blacks which are not stable and turn green on keeping and the stable 'ungreenable' black. The constitution of these polymeric compounds is discussed below (p. 56).

The nature of the products obtained depends on the oxidizing agent, and such agents can be divided into two classes. The first class gives monomolecular products and some dimolecular products, but no polymolecular products, while the second gives dimolecular and polymolecular products and no monomolecular products, with the exception of quinone which contains no nitrogen. The two classes differ fundamentally in their method of attack on the aniline molecule. The first class, of which examples are hydrogen peroxide and Caro's acid (permonosulphuric acid, H$_2$SO$_5$), give oxygen to the aniline molecule, while the second class, which contains the majority of oxidizing agents, take hydrogen from the amino group to form a free radical. Important examples of the second class are chromic acid, perdisulphuric acid (Marshall's acid, H$_2$S$_2$O$_8$), and lead peroxide; the latter is extremely important in these investigations because it can be used in the absence of water. The two classes will be discussed separately.

With oxidizing agents of the first class the first product that can be detected is phenylhydroxylamine, which probably arises by rearrangement of the amine oxide formed by direct addition of oxygen.[2]
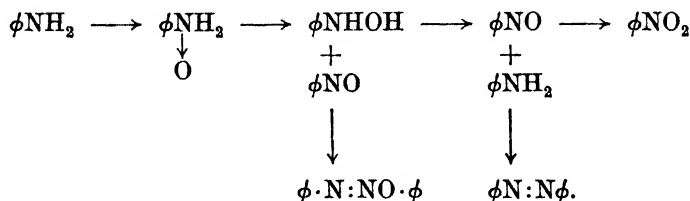
$$\phi \cdot NH_2 \longrightarrow \phi \cdot \underset{\overset{\mid}{O}}{NH_2} \longrightarrow \phi \cdot NHOH$$
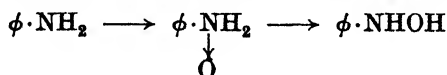
Phenylhydroxylamine is itself readily oxidized, so that it is never formed in quantity but is converted into nitrosobenzene or under more vigorous

[1] See especially E. Bamberger, *Ber.* 1898, **31**, 1522; S. Goldschmidt, ibid. 1920, **53**, 28; Goldschmidt and B. Wurzschmitt, ibid. 1922, **55**, 3216, 3220.

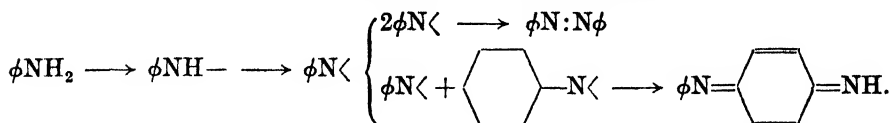[2] E. Bamberger and F. Tschirner, ibid. 1899, **32**, 1675.

conditions into nitrobenzene. Phenylhydroxylamine is also known to condense readily with nitrosobenzene to give azoxybenzene (p. 427) and nitrosobenzene condenses with aniline to give azobenzene, so that the appearance of these two bimolecular compounds among the products of oxidation by agents of this class is accounted for. All the products and their origin are shown in the following scheme:

$$\phi NH_2 \longrightarrow \phi NH_2 \longrightarrow \phi NHOH \longrightarrow \phi NO \longrightarrow \phi NO_2$$
$$\downarrow \qquad\qquad + \qquad\qquad +$$
$$O \qquad\qquad \phi NO \qquad\qquad \phi NH_2$$
$$\downarrow \qquad\qquad \downarrow$$
$$\phi \cdot N{:}NO \cdot \phi \qquad \phi N{:}N\phi.$$

Oxidizing agents of the second class give quite different results. No phenylhydroxylamine can be found as a primary product and its two oxidation products, nitroso- and nitrobenzene, are never formed under any conditions. The first compounds that can be isolated are the bimolecular substances azobenzene and phenyl quinone-diimine. The only monomolecular product that can be obtained is benzoquinone and that compound is only formed under vigorous conditions; it can be shown experimentally to arise from the oxidation of the polymolecular products which are so typical of oxidizing agents of this class and which never appear with those of the first class. Bamberger supposed that phenyl quinone-diimine, which, as it will appear, is the key to most of the other products, was formed by the interaction of phenylhydroxylamine and aniline followed by further oxidation:

$$H_2N\langle\bigcirc\rangle + HONH\phi \longrightarrow H_2N{-}\langle\bigcirc\rangle{-}NH\phi \longrightarrow HN{=}\langle\bigcirc\rangle{=}N\phi.$$
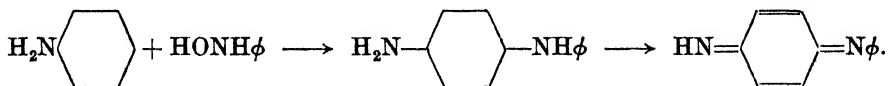
This view offers no explanation of the absence of the typical phenylhydroxylamine oxidation products, and the improbability of phenylhydroxylamine being an intermediate at all was demonstrated by Goldschmidt when he found that the action of copper on phenyldichloramine, $\phi \cdot NCl_2$ (see p. 66), also gives azobenzene and phenyl quinone-diimine as primary products. Phenylhydroxylamine cannot possibly be an intermediate in this case. Goldschmidt consequently suggested that the common term in the action of copper on the dichloramine and in that of an oxidizing agent of the second class on aniline was the free radical, $\phi \cdot N\langle$, formed from aniline by loss of hydrogen, and from the dichloramine by loss of chlorine. His scheme for the first stages of the oxidation is:

$$\phi NH_2 \longrightarrow \phi NH{-} \longrightarrow \phi N\langle \begin{cases} 2\phi N\langle \longrightarrow \phi N{:}N\phi \\ \phi N\langle + \langle\bigcirc\rangle{-}N\langle \longrightarrow \phi N{=}\langle\bigcirc\rangle{=}NH. \end{cases}$$

Such a view has the obvious advantage that it will account for the **great**

difference in the products formed by the two classes of oxidizing agents, by attributing to them entirely different mechanisms, and it will also account for the occurrence of azobenzene as a common term in both series. It finds very strong support in Goldschmidt's direct demonstration of the occurrence of a free radical in the oxidation of aniline. Free radicals which are not identical often unite immediately with one another (see pp. 389 and 463); the triphenylmethyl radical is known to be unaffected by lead peroxide or by aniline. Hence Goldschmidt and Wurzschmitt took a solution of aniline in dry ether and added to it hexaphenylethane which is partly dissociated into triphenylmethyl in solution. Air had to be excluded because it reacts with triphenylmethyl. When the mixture was shaken with lead peroxide, they obtained anilinotriphenylmethane which could only be formed by direct union of the radicals:

$$\phi NH— + —C\phi_3 \longrightarrow \phi NH \cdot C\phi_3.$$
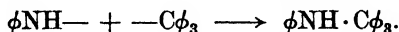
Phenyl quinone-diimine, HN=⟨⟩=Nϕ, a yellow solid, melting-point 89°, is a very reactive compound and can only be isolated when aniline is oxidized with permanganate under carefully regulated conditions. Its characteristic behaviour is to polymerize and some of the products usually obtained arise from the various ways in which the polymerization can take place. These products are not easy to investigate since many are of high molecular weight and sparingly soluble. The diimine can also react with the aniline present which has not been attacked to give other compounds. There appear to be two main possibilities in the polymerization: either the hydrogen atoms in the ortho position are involved, or else the hydrogen atom of the imino group. The first possibility leads to the trimolecular polymer (I) which is formed by the action of acetic acid or traces of hydrogen chloride on the diimine. This can be converted, by the action of aniline and acid into azophenine (II) and it seems probable that phenazines, the class of compounds to which Perkin's mauve belongs, are formed from these compounds.

I.   II.
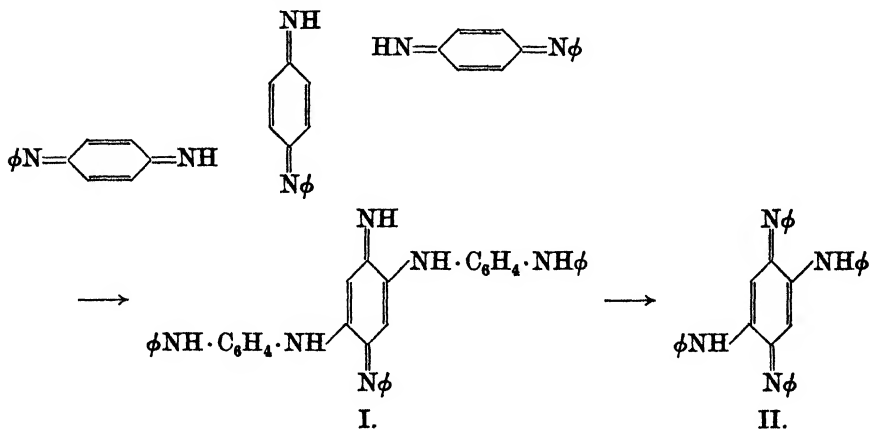
The second possibility leads to linear polymers. With a slight change in

the hydrogen-ion concentration, polymerization of the diimine gives, instead of the tripolymer (I), the dimolecular compound (III), which can be oxidized to t'ie di-quinone derivative (IV). The polymerization can then be repeated with this compound to give a substance which contains eight aniline residues, and this compound can be oxidized further with the formation of further quinone structures and so on.

$$2\,\phi N{=}\langle\quad\rangle{=}NH$$

$$\downarrow$$

III. $\phi N{=}\langle\quad\rangle{=}N{-}\langle\quad\rangle{-}NH{-}\langle\quad\rangle NH_2$

$$\downarrow \quad \text{oxidize}$$

IV. $\phi N{=}\langle\quad\rangle{=}N{-}\langle\quad\rangle{-}N{=}\langle\quad\rangle{=}NH$

$$\downarrow \quad \text{polymerize}$$

V. $\phi NH{-}\langle\quad\rangle{-}NH{-}\langle\quad\rangle{-}N{=}\langle\quad\rangle{=}N{-}\langle\quad\rangle{-}N{=}\langle\quad\rangle{=}N{-}\langle\quad\rangle{-}N{=}\langle\quad\rangle{=}NH$
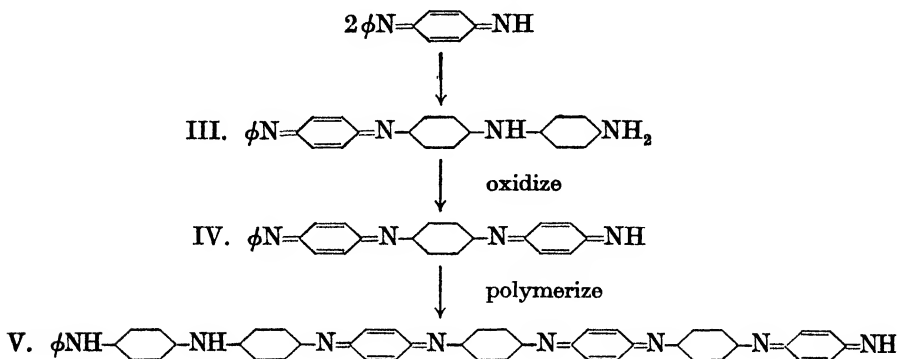
A product of the type of (V) can clearly exist in various states of oxidation which differ from one another in the number of benzenoid and quinonoid rings in the chain, and a series of compounds can be obtained from the oxidation of aniline which are related to one another in this way. They are called (in decreasing states of oxidation) perinigraniline, nigraniline, and emeraldine. The compound formed by reducing any of these to the state where all the rings are benzenoid and none quinonoid is leuco-emeraldine, a pale brown powder which does not melt below 350° and is insoluble in all solvents; it is stable in dry air, but is easily oxidized to emeraldine and further up the series. Whether the known series of compounds is correctly represented by formulae with eight aniline residues (such as (V), which may be nigraniline), or whether linear polymerization goes further and the actual compounds contain multiples of this structure, is unknown: the physical properties of the compounds do not lend themselves to determinations of molecular weight. However it seems clear that chains of this type exist in these compounds, because on vigorous oxidation and hydrolysis they are broken down with the formation of benzoquinone, $O{=}\langle\quad\rangle{=}O$, in which the ortho positions have been unattacked. The ordinary laboratory preparation of quinone is based on this fact.

All these compounds are deeply coloured, with the exception of the leuco compound which, of course, is not formed in the oxidation of aniline, but only by reduction of the other members of the series. Hence it was at one time supposed that they constitute the aniline black which is used as a dye-stuff. This is, however, hardly likely. Emeraldine and its congeners are indamines (see p. 102) and as such are unstable compounds; nigraniline, a blue-black powder, is decomposed on standing with acids, and perinigraniline, its further oxidation product, is quite unstable. The aniline black formed commercially in the fibre of various materials, the so-called

'ungreenable' black, is a very stable substance; if it were not, it would have little technical importance. These more stable black substances can be obtained from the emeraldine series by further oxidation in the presence of aniline and the latter seems to be necessary for their formation. Hence it seems likely that in the true aniline blacks the aniline has condensed with the linear polymers to form phenazine units which are known to be stable structures.
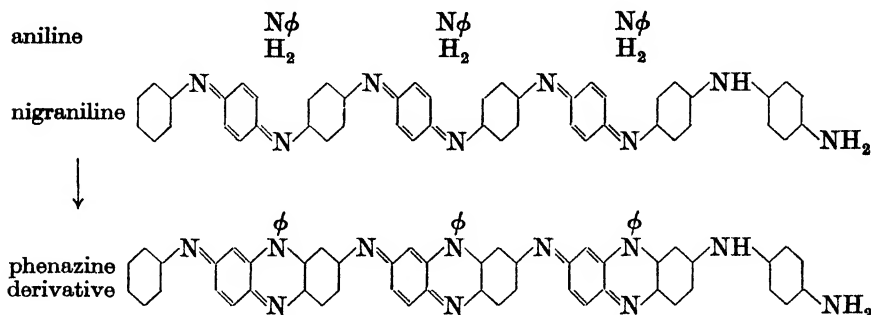
The length of the chain is unknown and may well be much longer than that shown in the formulae. In the technical production of ungreenable blacks the fabric is treated with a paste which contains aniline, an acid and an oxidizing agent such as sodium chlorate, or lead chromate, together with other compounds whose function is not understood, such as copper salts or potassium ferrocyanide and the colour developed by subjecting the fabric to steam.[1]

SUBSTITUTED ANILINES

These fall into two main divisions:

A. Those in which one or both of the hydrogen atoms of the amino group are replaced. This division comprises the N-alkyl and N-aryl anilines, which are the secondary and tertiary aromatic amines, and compounds such as the aromatic chloramines, nitramines, and N-acyl derivatives. Some of these are described in other parts of this book (nitramines, p. 454; anilides, p. 136).

B. Those in which one or more hydrogen atoms attached to the aromatic nucleus are replaced.

A. *Amines with Substituents attached to nitrogen*

N-alkylanilines

The primary base aniline can be converted into secondary and tertiary bases by many of the methods which have been described for the similar change in the aliphatic series. Thus alkyl halides heated with aniline give first the secondary base ϕNHAlk, and on further action the tertiary base ϕNAlk$_2$; alkyl sulphates and sulphonates such as dimethyl sulphate or

[1] For the constitution of aniline black, see A. G. Green and A. E. Woodhead, *J.C.S.* 1910, **97**, 2395; Green and S. Wolff, *Ber.* 1911, **44**, 2571; E. Grandmougin, *Rev. Chim. ind.* 1933, **42**, 202.

ethyl p-toluene sulphonate can be used. In reactions such as these a mixture of the secondary and tertiary compounds is often formed which sometimes cann.ot be separated by distillation because their boiling-points lie too close together (see Table, p. 59). The two can be separated easily by treating the mixture with acetic anhydride or benzene sulphonyl chloride with which only the secondary base reacts to give an amide. The amide is non-basic while the tertiary base is soluble in dilute mineral acid, and from the amide the secondary base can be recovered by hydrolysis. Several methods are known by which monoalkyl anilines can be obtained unaccompanied by tertiary bases. For example, acetanilide, $\phi \cdot NH \cdot COCH_3$, forms a sodium derivative which reacts readily with alkyl halides to give N-alkyl acetanilides and these can be hydrolysed with acids or alkalis to the secondary bases:

$$\phi \cdot NH \cdot COCH_3 \longrightarrow \phi \cdot NR \cdot COCH_3 \longrightarrow \phi \cdot NHR + HO_2C \cdot CH_3.$$

Again aniline condenses with aldehydes and, less readily, with ketones to form the so-called Schiff's bases or anils (see p. 65) and these can be reduced to secondary bases: the reduction is often carried out with sodium and alcohol or else electrolytically.

$$\phi \cdot CHO + H_2N\phi \longrightarrow \phi \cdot CH:N\phi \longrightarrow \phi \cdot CH_2 \cdot NH\phi$$
benzylaniline
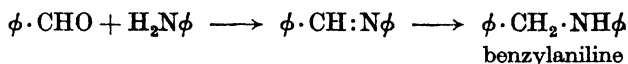
The simpler aliphatic aldehydes, in particular formaldehyde, give more complicated condensation products with primary aromatic amines (see p. 65) and these on reduction give mixtures of the primary, secondary, and tertiary bases.[1] The reduction of the formaldehyde-aniline compound, the so-called anhydroformaldehyde-aniline, with zinc dust in alkaline solution, however, gives under suitable conditions very little dimethyl aniline and has been used for obtaining monomethylaniline.[2]

There are two other methods which can be used for the preparation of an N-alkyl aniline from a Schiff's base. When the latter is treated with a Grignard reagent an addition complex is formed which is decomposed by water to give a secondary amine, often in very good yield:[3]

$$\phi N:CH\phi + RMgI \longrightarrow \underset{IMg}{\overset{\phi}{\diagdown}} N-CH \underset{\phi}{\overset{R}{\diagup}} \overset{H_2O}{\longrightarrow} \phi NH \cdot CH \underset{\phi}{\overset{R}{\diagup}} + Mg \underset{OH}{\overset{I}{\diagup}}.$$
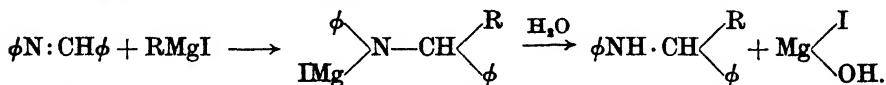
The second method consists in treating the Schiff's base with methyl iodide[4] or dimethyl sulphate,[5] when an unstable quaternary salt is formed; this is very easily hydrolysed by water with formation of the N-methyl aniline:

$$\phi N:CH\phi + MeI \longrightarrow [I] \underset{Me}{\overset{\phi}{\diagdown}} N:CH\phi \longrightarrow \underset{Me}{\overset{\phi}{\diagdown}} NH + \phi CHO.$$
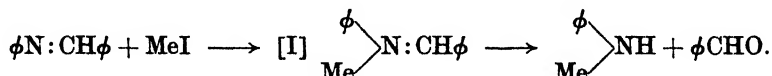
[1] J. G. Miller and E. C. Wagner, *J. Amer. C. S.* 1932, **54**, 3698.
[2] P. F. Frankland, F. Challenger, and N. A. Nicholls, *J.C.S.* 1919, **115**, 198.
[3] M. Busch, *Ber.* 1904, **37**, 2691; Busch and A. Rinck, ibid. 1905, **38**, 1761.
[4] H. Decker and P. Becker, *Annalen*, 1913, **395**, 362.
[5] K. Kindler and W. Peschke, *Arch. Pharm.* 1932, **270**, 356.

The N-alkyl anilines are of considerable importance as dye-stuff intermediates; they are usually prepared commercially by heating aniline sulphate or hydrochloride with the required aliphatic alcohol under pressure to temperatures of the order of 170–180°. In many cases catalysts are added to aid the reaction, notably copper powder, copper or calcium chloride, sodium bromide, and so on. There is little doubt that the reaction proceeds by the intermediate formation of the alkyl halide or sulphate which then reacts with the aniline.

The N-alkylanilines are liquids with a characteristic and unpleasant smell; they are only very sparingly soluble in water and distil without decomposition.

	b.p.		m.p.	b.p.
Monomethylaniline	194°	Dimethylaniline	+2·1°	192°
Monoethylaniline	206	Diethylaniline	39	216
Monopropylaniline	222	Dipropylaniline	..	245

They behave as monoacidic bases but the introduction of alkyl groups attached to nitrogen does not appear to increase their basicity very markedly and their apparent dissociation constants (the true constants are not known: see p. 30) are of the same order of magnitude as that of aniline. The monoalkyl compounds are secondary amines and resemble the aliphatic secondary bases in many of their reactions; thus they react with acid chlorides and anhydrides to form N-acyl compounds and with nitrous acid they give nitrosamines or N-nitroso compounds which are described later (p. 451):

$$\begin{array}{c}\phi \\ R\end{array}\!\!>\!\!NH \longrightarrow \begin{array}{c}\phi \\ R\end{array}\!\!>\!\!N\cdot NO.$$
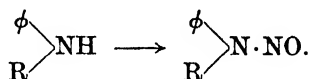
In reactions involving nuclear substitution they resemble aniline closely. The dialkyl compounds are tertiary bases and, as such, form quaternary ammonium salts with alkyl halides and similar compounds. The reaction takes place with very great differences in speed according to the nature of the alkyl halide and of the alkyl groups in the tertiary amine: thus methylpropylaniline reacts with benzyl iodide with evolution of heat to form methyl-propyl-phenyl-benzylammonium iodide, but the same product is only formed in small yield when methylbenzylaniline is heated with propyl iodide under pressure. Being tertiary amines the dialkylanilines can be oxidized to amine oxides, which, since they are derived from aromatic amines, are usually called aniline oxides (see p. 166).

The dialkylanilines differ considerably from the aliphatic tertiary bases in that they undergo a series of reactions in which the hydrogen atoms of the nucleus are involved. As is mentioned below in discussing the nuclear substitution reactions of aniline, the hydrogen atoms in the para and ortho positions to the primary amino group are extremely reactive. This is also true in a compound like dimethylaniline and it is especially marked for the following reason. Certain reagents which react with the primary amino group of aniline cannot react with the dimethylamino group of

dimethylaniline, which contains no hydrogen attached to nitrogen, and so they react with the activated nuclear hydrogen atoms. The best-known example of such a reaction is that with nitrous acid; an aliphatic tertiary amine is unaffected by that acid, but dimethylaniline gives the C-nitroso compound, p-nitrosodimethylaniline (see p. 219):

$$Me_2N-\langle\ \rangle \longrightarrow Me_2N-\langle\ \rangle-NO.$$
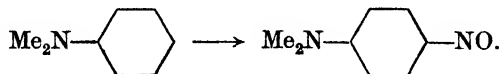
Another example is condensation with an aldehyde; aniline gives a Schiff's base, the amino group entering into the reaction: dimethylaniline gives the leuco-base of malachite green (see p. 83), the para hydrogen atoms of two molecules being eliminated as water:

$$2\,Me_2N-\langle\ \rangle + \phi\cdot CHO \longrightarrow Me_2N-\langle\ \rangle-CH\phi-\langle\ \rangle-NMe_2.$$
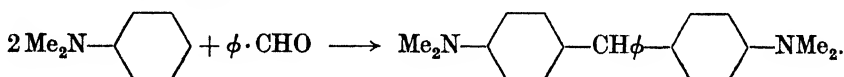
An acid chloride cannot react by substitution with the dialkylamino group, but carbonyl chloride reacts with dimethylaniline to give the so-called Michler's ketone, an important dye-stuff intermediate:

$$2\,Me_2N-\langle\ \rangle + COCl_2 \longrightarrow Me_2N-\langle\ \rangle-CO-\langle\ \rangle-NMe_2.$$
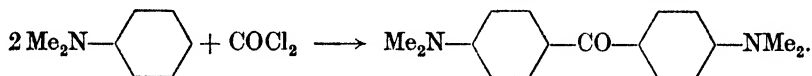
The hydrochlorides of the mono- and dialkylanilines undergo an interesting change on heating (the Hofmann-Martius reaction). Under ordinary pressure in a current of hydrogen chloride they lose alkyl groups as alkyl chloride, but if the heating is carried out in a closed vessel at about 300°, the alkyl groups appear to migrate to the nucleus with the production of primary amines, homologues of aniline; thus methylaniline is converted into p-toluidine. This change is discussed later (p. 78). A similar change takes place with the aromatic quaternary ammonium halides.

Purely Aromatic Amines

Diphenylamine, ϕ_2NH, is the simplest purely aromatic secondary amine. It was first obtained by Hofmann in 1863 by the destructive distillation of certain triphenylmethane dyes. It is prepared by heating aniline and its hydrochloride together under pressure at 210–240° for 30–35 hours:

$$\phi\cdot NH_2 + \phi\cdot NH_3[Cl] \longrightarrow \phi_2NH + NH_4Cl.$$

Compounds of this class can also be obtained by heating aniline or one of its homologues with phenols in presence of zinc chloride or antimony trichloride. The halogen atom in a compound such as bromobenzene is much less reactive than in an aliphatic halide, so that the reaction between a primary aromatic amine and an aryl halide to form a secondary aryl amine does not take place at all readily. It is catalysed, however, at 200–220° by finely divided copper (copper bronze) like other reactions of the aryl halides, and diphenylamine and its homologues can be prepared

by boiling bromobenzene with a primary amine in nitrobenzene solution in presence of copper:

$$\phi NH_2 + Br\phi \longrightarrow \phi_2 NH + HBr.$$
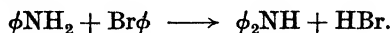
If there is a carboxyl group in the ortho position to the halogen atom, the reaction proceeds more easily, so that it is sometimes advantageous to use o-chlorobenzoic acid and copper; the carboxylic acid thus formed usually loses carbon dioxide quite readily on heating.[1]
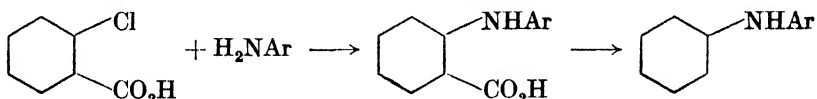
Sometimes the reaction takes place more readily if cuprous iodide is used instead of copper, or if the acetyl derivative of the amine is used, or if solid potassium carbonate is added.[2]

The simple diarylamines are solids which boil at high temperatures without decomposition.

	m.p.	b.p.
Diphenylamine	52·8°	302°
Phenyl-p-tolylamine . . .	89	318
Di-p-tolylamine	79	330

They are insoluble in water, and are such weak bases that they do not dissolve in dilute aqueous acids. Diphenylamine gives a hydrochloride with strong hydrochloric acid, but this is at once hydrolysed by water with precipitation of the free base. On the other hand, diphenylamine is distinctly more acidic than the mixed aromatic-aliphatic secondary amines, and its sodium salt, $\phi_2 NNa$, and potassium salt, $\phi_2 NK$, are known. The former is best obtained by the action of diphenylamine on sodamide and the latter by dissolving potassium in molten diphenylamine. In many ways diphenylamine behaves as a typical secondary amine. It is converted into acetyl-diphenylamine, $\phi_2 N \cdot CO \cdot CH_3$, by the action of acetyl chloride or acetic anhydride, and addition of sodium nitrite to its solution in alcoholic hydrochloric acid gives diphenyl-nitrosamine, $\phi_2 N \cdot NO$, which does not differ in its simple reactions from the nitrosamines derived from other secondary bases.

If sodium diphenylamine is treated with iodine, tetraphenyl-hydrazine is formed and the same compound can be obtained by the action of various oxidizing agents on diphenylamine in neutral solution. In these two reactions the first product is the free radical $\phi_2 N$, formed by loss of sodium in one case and of hydrogen in the other; this free radical largely associates to the hydrazine but in solution is capable of separate existence (see p. 388).
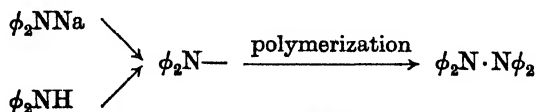
[1] F. Ullmann, Ber. 1903, 36, 2382.   [2] I. Goldberg, Ber. 1907, 40, 4541.

When diphenylamine is dissolved in concentrated sulphuric acid and a small quantity of an oxidizing agent is added, a deep blue colour develops; the majority of oxidizing agents give this result, but nitrous acid is especially effective. This fact has a number of applications; the colour can be used as a delicate test for diphenylamine or for nitrous acid, and on it have been based colorimetric methods for the quantitative estimation of traces of the latter. It can also be used as an internal indicator in the titration of a ferrous salt with standard bichromate solution;[1] the solution must be strongly acid, phosphoric acid being often used, and the diphenylamine is conveniently replaced by the sodium salt of its sulphonic acid which is soluble in water. The ferrous ion is oxidized more readily than the diphenylamine, so that the deep colour of the diphenylamine oxidation-product appears immediately all the iron has been oxidized to the ferric state. The constitution of the blue compound was a matter of uncertainty for many years, but has been established by the work of Wieland and Kehrmann.[2] It was at first thought that the diphenylamine is oxidized to tetraphenylhydrazine as in neutral solution; tetraphenylhydrazine gives deeply coloured compounds with acids (see p. 391), and this seemed to give a satisfactory explanation of the formation of the blue colour. The same colour, however, is obtained by oxidizing methyldiphenylamine, ϕ_2NMe, and triphenylamine, ϕ_3N, which are tertiary bases and cannot be oxidized to hydrazines, and, on the other hand, di-p-tolylamine, $(Me \cdot C_6H_4)_2$NH, which can be oxidized to a hydrazine in neutral solution, gives no blue colour with nitrous acid in strong sulphuric acid, but only a yellow one. The point of attack of the oxidizing agent thus seems to be the p-hydrogen atom of a benzene nucleus and not the imino hydrogen atom. This conclusion was confirmed by reducing the blue solution with zinc dust after dilution with water; N,N'-diphenylbenzidine, ϕNH$\cdot C_6H_4 \cdot C_6H_4 \cdot$NH$\phi$, was obtained. The coloured compound must be a derivative of this substance. An alternative mechanism for the formation of this benzidine is the rearrangement of tetraphenylhydrazine, which would be an example of the well-known benzidine rearrangement (see p. 385). Wieland, however, found that tetraphenylhydrazine gives very little of the benzidine in strong sulphuric acid, and such a mechanism is definitely excluded by the colour formation with methyldiphenylamine which cannot be oxidized to a hydrazine. That there should be two ways in which diphenylamine can be oxidized, at the imino group in neutral solution and at the para carbon atom in strongly acid solution, is hardly surprising: it is analogous to the very different reactivity of the amino group, —NH$_2$, and the ion —NH$_3^+$.

$$\phi\overset{+}{\text{N}}\text{H}_2\!\!-\!\!\langle\bigcirc\rangle + \langle\bigcirc\rangle\!\!-\!\!\overset{+}{\text{N}}\text{H}_2\phi \longrightarrow \phi\overset{+}{\text{N}}\text{H}_2\!\!-\!\!\langle\bigcirc\rangle\!\!-\!\!\langle\bigcirc\rangle\!\!-\!\!\overset{+}{\text{N}}\text{H}_2\phi$$
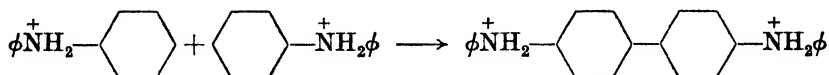
[1] J. Knop, *J. Amer. C. S.* 1924, **46**, 263.

[2] The more important papers are: F. Kehrmann and S. Micewicz, *Ber.* 1912, **45**, 2641; H. Wieland, ibid. 1913, **46**, 3296; 1919, **52**, 886; F. Kehrmann and G. Roy, ibid. 1922, **55**, 156.

Determination of the constitution of the blue compound is not a simple matter. It is clearly the salt of an oxidation product of diphenylbenzidine and is analogous to the unstable dyes obtained by oxidizing p-phenylene diamine and its derivatives in acid solution, the so-called Wurster salts. Complete oxidation of the benzidine gives the salt of a diquinone diimine,

$$\phi \overset{+}{\text{N}}\text{H} = \bigbigcirc = \bigbigcirc = \overset{+}{\text{N}}\text{H}\phi,$$
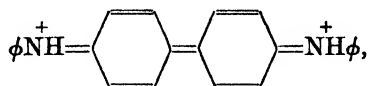
and both this and its free base are weakly coloured compounds. The blue colour occurs at a half-way stage in the oxidation when each benzidine molecule has lost one electron. The constitution of such compounds is discussed in detail below (p. 98).

The purely aromatic tertiary amines, such as triphenylamine, can be obtained by methods similar to those used for the preparation of the aromatic secondary bases; aromatic halogen compounds are heated with the secondary bases to a high temperature in presence of copper bronze or soda lime. They are solids which distil at atmospheric pressure at temperatures above 350° without any decomposition. They show no ordinary basic properties whatever and quaternary ammonium salts containing three, or even two, aromatic residues attached to the nitrogen atom are unknown. For all their stability under most conditions they are extremely sensitive to the halogens and to acid oxidizing agents, and their behaviour towards these reagents indicates that they can be transformed very readily into free radicals. Wieland found that on addition of chlorine or bromine to a solution of tritolylamine in inert solvents, deeply coloured blue salts were formed; these are unstable, but the bromine compound can be analysed and shown to contain three atoms of bromine to one of the amine. Further, although tri-p-tolylamine is completely unaffected by acids, if an oxidizing agent is present as well, deep-blue salts can be obtained; thus, if to the amine dissolved in a mixture of benzene and ligroin picric acid and dry lead peroxide are added, a deep-blue crystalline picrate separates out. These blue compounds are attacked at once in the cold by all reducing agents and the original amine regenerated. Triphenylamine behaves differently towards acids and oxidizing agents; a blue colour appears, but reduction does not give the amine back again; tetraphenylbenzidine, $\phi_2 \text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{C}_6\text{H}_4 \cdot \text{N}\phi_2$, is formed. The blue salt from triphenylamine must be similar to that from diphenylamine, and the oxidizing agent must have attacked the para carbon atom of one nucleus. No such explanation is possible for the blue salts from tritolylamine in which the oxidizable para position is blocked by a methyl group; their reduction to the original amine shows clearly that they are formed from one molecule of the amine and not from two or more molecules.

The nature of these coloured salts of tritolylamine has been disclosed by the ingenious work of E. Weitz and H. W. Schwechten.[1] The behaviour

[1] *Ber.* 1926, **59**, 2307.

of the amine recalls that of a noble metal such as copper or silver, in that these metals can combine with the halogens to form salts, but cannot displace the hydrogen of an acid to give a salt of the acid unless an oxidizing agent is present to unite with the hydrogen; the amine can be described as metallic in its salt formation. When a metallic atom becomes a kation, it loses an electron either to the halogen which becomes an anion or to the oxidizing agent; hence it would appear that the same thing happens with the nitrogen atom of the amine, an electron is lost and a kation remains. On this view the constitution of the kation of these coloured salts is that of a free radical, there being one less electron than is needed for a compound of normal valency. The formation of a free radical ion of constitution $[Ar_3N]^+$ is hardly surprising. As is discussed later (p. 388), tetra-aryl hydrazines partially dissociate in solution into free radicals which are Ar_2N. The radical-ion is related to this uncharged radical in precisely the same way as the tetra-methylammonium ion $[Me_4N]^+$ is related to trimethylamine Me_3N; the salt $[Ar_3N]^+X$ can be considered as the quaternary salt of the free radical Ar_2N. They are not ammonium salts, because the covalency of the nitrogen atom is not four, but three: Weitz has used the convenient name, aminium salts. It should be noticed that in the kation $[Ar_3N]^+$ the nitrogen atom is united to three aromatic residues and has seven valency electrons; it is thus exactly similar to the carbon atom in the uncharged free radical triphenylmethyl, ϕ_3C. The stability of these radicals arises from the fact that they are resonance-hybrids of a number of structures which contain benzenoid and quinonoid rings, a point which is discussed in greater detail in the account of the nitrogen radicals of the type Ar_2N (p. 390). The deep colour of the aminium radicals is also connected with this same fact, since resonance between benzenoid and quinonoid structures often seems to give strong absorption in the visible part of the spectrum; examples of this phenomenon are the Wurster salts (p. 98), the triphenylmethane dyes (p. 82), and the cyanine dyes (p. 561).

On this view of the constitution of the coloured salts, the blue compound formed from tritolylamine and bromine must be formulated $[Ar_3N]Br_3$, an aminium perbromide; many organic bases form perbromides of this type. One of the more stable aminium salts is obtained by the interaction of tritolylamine with the free radical chlorine tetroxide, ClO_4; the two combine immediately and quantitatively to give the aminium perchlorate $[Ar_3N]ClO_4$ by simple transfer of one electron. The salt forms a deep violet-blue crystalline powder which can be kept for some days without decomposition, but explodes above its melting-point (123°). There is considerable support for the radical nature of the ions of these salts in the fact that similar salts are known which are related to the other well-known series of nitrogen free radicals, the hydrazyls, $\phi_2N \cdot N\phi$, just as the aminium salts are related to the divalent nitrogen radicals (see p. 392).

Anils or Schiff's Bases.

The compounds in which both hydrogen atoms of the amino group of an aromatic amine are replaced by one hydrocarbon residue are known as anils or Schiff's bases. An aromatic aldehyde, such as benzaldehyde, condenses very readily when mixed with aniline to give such a compound:

$$\phi CHO + H_2N\phi \longrightarrow \phi CH:N\phi + H_2O.$$
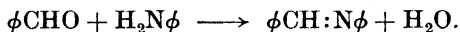
Similar compounds can be obtained from ketones, but the condensation does not take place so readily: a higher temperature is needed and zinc chloride or iodine must be used as catalysts. Anils can also be obtained in other ways, as by the condensation of a keto-dichloride, R_2CCl_2, with an aniline, or of a nitroso compound with a substance containing a reactive methyl group (see p. 209):

$$\phi \cdot NO + H_3C \cdot R \longrightarrow \phi \cdot N : CHR.$$
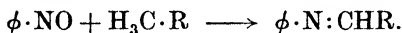
The Schiff's bases are crystalline compounds which can often be distilled without decomposition. They are weak bases and form hydrochlorides in non-aqueous solvents, but their characteristic behaviour is the great ease with which they are hydrolysed by aqueous acids to the aniline and carbonyl compound from which they are derived. They are stable to aqueous alkalis. The action of methylating agents and of Grignard reagents on Schiff's bases has been mentioned above (p. 58).

The substances obtained by condensing aliphatic aldehydes with aniline are more complex. Aniline condenses rapidly with formaldehyde and the product is a mixture which can be separated into two main fractions, one being soluble and the other insoluble in organic solvents. The molecular weight of the soluble compound corresponds to $(\phi N : CH_2)_3$ and on reduction it gives a mixture of aniline, methylaniline, and dimethylaniline. The formation of the latter shows that the compound contains nitrogen attached to two carbon atoms and the structure of the compound is most probably that shown in (I). The insoluble compound must be of very high molecular weight: it is insoluble in all solvents and decomposes without melting above 210°; the essential element of its structure is probably a long chain as in (II).[1] The soluble compound partially changes into the

I.
$$\begin{array}{c} \text{N}\phi \\ \text{CH}_2 \quad\quad \text{CH}_2 \\ | \quad\quad\quad | \\ \text{N}\phi \quad\quad \text{N}\phi \\ \text{CH}_2 \end{array}$$
   II. $-\text{N}\phi-\text{CH}_2-\text{N}\phi-\text{CH}_2-\text{N}\phi-\text{CH}_2-$
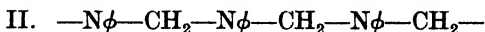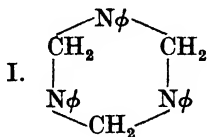
insoluble on standing or in solvents. Acetaldehyde and aniline also give a mixture of polymers, but the main product of their interaction at a low temperature is of a different type from that formed from formaldehyde; it contains the residue of one molecule of aldehyde to two of the amine and has the formula $Me \cdot CH(NH\phi)_2$. All these compounds can be hydrolysed with aqueous acids to aniline and the aldehyde.

[1] J. G. Miller and E. C. Wagner, *J. Amer. C. S.* 1932, **54**, 3698.

Of the other derivatives of aniline in which a substituent has replaced a hydrogen atom of the amino group, the acyl derivatives, $\phi \cdot NH \cdot CO \cdot R$, are substituted amides and are described in the chapter dealing with those substances (p. 136); the nitramines, $\phi \cdot NH \cdot NO_2$, contain two linked nitrogen atoms and will be found in Chapter XIV (p. 454). The phenylmonochloramines, $\phi \cdot NHCl$, and the dichloramines, $\phi \cdot NCl_2$, contain chlorine united to nitrogen; the monochloramines are probably intermediates in the action of hypochlorous acid on aniline, but have not been isolated. The dichloramines can be prepared, but are very unstable compounds.[1] Phenyldichloramine can be obtained as a thick orange-coloured oil by the action of an ethereal solution of hypochlorous acid on aniline at $-20°$. It explodes if it is removed from the freezing mixture. The introduction of negative substituents into the nucleus increases the stability of the dichloramines, and those derived from the three nitroanilines are crystalline compounds which can be kept for a day at $-79°$, but soon decompose at room temperature. Pentachlorophenyl-dichloramine, $C_6Cl_5 \cdot NCl_2$, is stable at room temperature in the absence of moisture and 4-hydroxy-2,3,5,6-tetrachlorophenyl-dichloramine, which can be obtained by the action of sulphuryl chloride on p-amino-phenol,[2] can be distilled in steam.

The reactions and decomposition of the phenyldichloramines show several points of interest. Like most N-chlor compounds they behave as oxidizing agents and immediately liberate iodine from potassium iodide. But reducing agents do not convert them into the amine from which they are derived; in this respect they differ from nitrogen trichloride and the aliphatic chloramines, which give ammonia and an aliphatic amine respectively.

The products obtained from phenyldichloramine itself are azobenzene and phenyl quinone-diimine, $\phi N{=}\langle\!\!\!\!\!\bigcirc\!\!\!\!\!\rangle{=}NH$. These same two compounds are also the sole products of the action of a large number of other substances, such as copper powder, caustic soda, aniline, and all other bases. The common term among all these substances is that they react with chlorine, and it is clear that in these reactions the dichloramine simply loses a molecule of chlorine and becomes a free radical, $\phi N{<}$, which then polymerizes either to azobenzene or to phenyl quinonediimine.

$$2\,\phi NCl_2 \longrightarrow 2\,\phi N{<} \begin{array}{l} \nearrow \phi N{:}N\phi \\ \\ \searrow \phi N{=}\langle\!\!\!\!\!\bigcirc\!\!\!\!\!\rangle{=}NH \end{array}$$
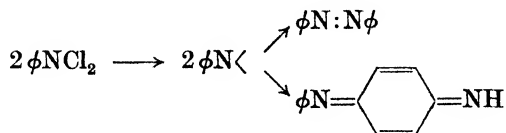
Azobenzene and the diimine are the two primary products formed in the action of certain oxidizing agents on aniline and are formed in that reaction by polymerization of the same radical, $\phi N{<}$ (see p. 54). With the substituted phenyldichloramines, the product obtained with the various

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[1] S. Goldschmidt, *Ber.* 1913, **46**, 2728; Goldschmidt and L. Strohmenger, ibid. 1922, **55**, 2450. [2] W. Eller and L. Klemm, ibid. 1922, **55**, 217.

reagents mentioned is almost entirely the azo compound; the negative substituents reduce the reactivity of the nucleus so that polymerization to the quinone derivative, which involves nuclear reactivity, does not take place.

If phenyldichloramine is treated with acids, and especially hydrogen chloride in ether, the chlorine atoms appear to migrate from the nitrogen to the nucleus and 2,4-dichloraniline and a little 2,4,6-trichloraniline are formed. In this the compound resembles the much more stable N-chloracetanilide, $\phi \cdot NCl \cdot COMe$, which with hydrogen chloride becomes p-chloracetanilide, $Cl \cdot C_6H_4 \cdot NH \cdot COMe$. In the latter case it is known that the mechanism of the reaction involves the liberation of chlorine followed by chlorination of the nucleus:

$$\phi NCl \cdot COMe + HCl \longrightarrow \phi NH \cdot COMe + Cl_2 \longrightarrow HCl + Cl \cdot C_6H_4 \cdot NH \cdot COMe.$$
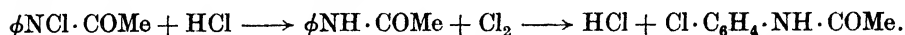
Hence it seems probable that there is no true migration of the chlorine atoms in the case of the dichloramine, but a similar intermediate formation of chlorine.[1]

B. *Aromatic Amines with Nuclear Substituents*

In many of the reactions of the aromatic amines there is direct substitution of a hydrogen atom attached to a carbon atom of the ring by some other entering group. In these reactions the entering group usually takes up a position in the ring which is para or ortho to the amino group, and, as with other ortho-para directing groups, in most cases of monosubstitution more of the para than of the ortho compound is formed. It is impossible, however, to make a generalization as to the ratio of para to ortho-substituted amine formed, because this ratio depends on the conditions of the reaction and the nature of the substituting reagent used; an example which has been quoted already (p. 12) is the nitration of acetanilide by nitric acid and by acetyl nitrate, the former giving mainly para-nitro-acetanilide and the latter mainly the ortho compound. Substitution reactions take place extremely readily with most aromatic amines; even in very dilute aqueous solution aniline reacts rapidly with bromine to give 2,4,6-tribromaniline, in which a bromine atom has entered the para and both ortho positions. Only certain types of groups can be introduced directly into the nucleus of an aromatic amine: aniline and its derivatives can be nitrated, brominated, and sulphonated, and they will react with aromatic diazo compounds to give C-azo derivatives, but other groups such as —OH, —NH₂, and —CN cannot be introduced by direct substitution.

These three facts, (*a*) that the amino group is ortho-para directing, (*b*) that when substitution occurs, it takes place readily, and (*c*) that the aromatic amines react with kationoid reagents such as bromine and nitric acid and not with anionoid reagents such as sodamide, are closely related to one another and arise from the particular nature of the interaction between the amino group and the aromatic nucleus. The free

amine contains a nitrogen atom with an unshared pair of electrons, and that it is these which are involved in the interaction is clearly shown by the fact that when the nitrogen atom has no unshared pair of electrons, as in the quaternary salt $\phi NMe_3[Br]$, the whole of the behaviour towards substituting reagents is different. This phenomenon is discussed more fully below. The interaction of the amino group with the nucleus is consequently held to consist in a process whereby the unshared electrons are shared or tend to become shared with the ring system; this leads to the carbon atoms in the ortho and para positions becoming centres of greater electronic density and hence becoming activated towards kationoid reagents[1]. This process is often shown as in the following diagrams, in which the arrows indicate the direction of the movement of the electrons.
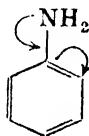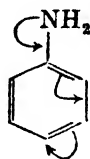
Ortho-activation   Para-activation.

This view accounts satisfactorily for the three inter-related facts; substitution takes place in the ortho and para positions because it is there that the electronic density is large; substitution takes place more easily than with benzene itself, because the electronic density which results from the electromeric change is greater than in benzene; finally an anionoid reagent such as the hydroxyl ion is unlikely to react with a negative carbon atom.

The electronic shift which causes the activation of the ortho and para positions in aniline towards kationoid reagents can be regarded in another light. The unshared electrons of the nitrogen atom can become fully shared by the group $-NH_2$ being transformed into the group $=NH_2^+$; for such a process to take place one of the carbon atoms of the ring must gain a negative charge. There are three arrangements possible, in two of which an ortho carbon atom is negatively charged, and in the other a para atom.
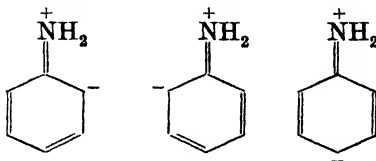
In these three structures the arrangement of the atoms is identical with that in the formula of aniline as usually written, but there is a difference in the distribution of electrons. Hence there is the possibility of resonance between these three structures and the two ordinary Kekulé structures for aniline, and the actual state of the molecule of aniline may well be that

[1] See R. Robinson, *Two Lectures on an 'Outline of an Electrochemical Theory of the Course of Organic Reactions'*, Institute of Chemistry, London 1932; *J. Soc. Dyers and Colour.*, 1934, Jubilee Number, p. 65; Institut Solvay, *Rapport 'Constitution et configuration des molécules organiques'*, Paris, 1931, p. 423.

of a resonance-hybrid, in the participating states of which there are negatively charged carbon atoms in the ortho and para positions. It is thus possible to link up with the phenomenon of resonance the electronic shift which must be postulated to account for the behaviour of aniline in substitution reactions, but which clearly does not proceed to completion and to the formation of an actual internal salt (zwitterion) of the kind shown in the formulae above. From this point of view the absence of any activation of a carbon atom in the meta position is due to the impossibility of a structure in which that carbon atom carries a negative charge. The structure would be:
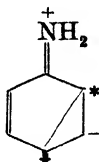
Such a structure, which is analogous to that of the unknown metaquinones, is impossible because the distance between the two carbon atoms marked with asterisks is too long for the single bond to be formed.

Although in the majority of substitution reactions of the aromatic amines the substituent enters the para or ortho positions, when the reaction is carried out in strongly acid solution the meta-substituted product is formed. The reason for this reversal is immediately clear from the fact that with the trimethylphenylammonium ion, $\bigcirc NMe_3^+$, meta-substitution alone takes place.[1] If the primary amine is present only as the kation, $Ar \cdot NH_3^+$, the nitrogen atom has no unshared electrons and the position taken up by the entering group is determined by the positive charge on the nitrogen atom. In all compounds where a positively charged atom is directly attached to a benzene ring a substituent takes up the meta position with respect to that atom; examples are the sulphonium ion, $\phi \cdot SMe_2^+$, and the iodonium ion, $\phi_2 I^+$. The positively charged atom initiates an electron shift which is of the opposite kind to that which occurs in the free base $Ar \cdot NH_2$, so that the meta positions are activated towards the ordinary kationoid reagents such as nitric acid or the halogens. As the positive charge is moved farther from the ring by interposing a saturated carbon chain, its influence becomes weaker and the amount of meta-substituted product is smaller: this is well shown in the following scheme in which the figures indicate the percentage of m-nitro compound formed in nitration.[2]
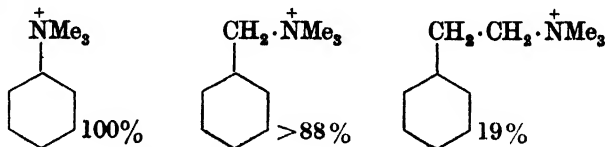
[1] D. Vorländer and E. Siebert, *Ber.* 1919, **52**, 283.

[2] H. R. Ing and R. Robinson, *J.C.S.* 1926, 1655; F. R. Goss, C. K. Ingold and I. S. Wilson, ibid., p. 2440.

In general ortho-para substitution takes place much more rapidly and easily than meta-substitution; for example 2,4,6-tribromaniline is formed almost instantan᾽ ously by the bromination of aniline in dilute aqueous solution at room temperature, while in the nitration of nitrobenzene, a substitution reaction governed by the meta-directing nitro group, 1,3,5-trinitrobenzene is only formed in any quantity when the reaction mixture contains large excess of nitric acid and is heated to 110° for several days. As a consequence of this fact large excess of a strong acid is necessary in order to obtain predominant meta-substitution in the aromatic amines. They are weak bases and even in the presence of excess of an acid there is a small concentration of the free base formed by salt hydrolysis; this free base is more rapidly attacked by the substituting agent in the para and ortho positions than the anilinium ion in the meta position, and hence the product may contain very little of the meta product.

In the preparation of many substituted anilines by direct substitution it is best to use an acyl derivative of the amine rather than the free amine itself, and the one most commonly employed is the acetyl derivative, $Ar \cdot NH \cdot CO \cdot CH_3$. There are two reasons for this. Firstly, the acetyl group serves to protect the amine group against secondary reactions. For example, aniline is easily oxidized and a reagent such as nitric acid is a strong oxidizing agent; an anilide is much less easily oxidized than free aniline and hence nitration of an anilide gives a product much less contaminated with oxidation products. The second reason for acetylating the amine before substitution is to control the extent of substitution. Thus in the direct bromination of aniline it is almost impossible to avoid the formation of considerable quantities of tribromaniline; with acetanilide the bromination does not take place so readily and mono-bromacetanilide can be obtained in good yield. That substitution takes place in acetanilide less readily than in aniline arises from the same causes which make acetanilide less basic than aniline. The activation of the para and ortho positions in the ring is due to the unshared pair of electrons of the nitrogen atom and it is also these electrons which are involved in salt-formation. When the acetyl group has been introduced before substitution for either of these purposes, it can be easily removed later by hydrolysis with a mineral acid or base.

A large number of aromatic amines, in which one of the amino-hydrogen atoms has been replaced by another group, undergo reactions on heating or on treatment with various reagents, in which the group attached to nitrogen appears to migrate to a carbon atom of the ring with the formation of a nuclear substituted amine. The formation of chloranilines from phenyldichloramine, ϕNCl_2, has been mentioned above (p. 67) and other examples will be found in later sections (e.g. $\phi \cdot NHMe \rightarrow Me \cdot C_6H_4 \cdot NH_2$, p. 77; $\phi \cdot NMeNO \rightarrow ON \cdot C_6H_4 \cdot NHMe$, p. 452). For this reason it has been held that the primary process of a substitution reaction of an aromatic amine is the formation of an N-substituted compound which then undergoes intramolecular rearrangement to give the C-substituted product. It

is very unlikely that this is in general the actual mechanism of substitution. In some cases the mechanism of these apparent migrations has been investigated and it has been shown that they do not proceed by a purely intramolecular, and hence unimolecular, reaction, but that they consist of two stages; first, the N-substituted aniline is decomposed, usually by the reagent which brings about the reaction, into the free amine and another substance, and then direct substitution of the free amine takes place. An example of such a reaction where the mechanism is known is the conversion of diazo-aminobenzene into amino-azobenzene which is discussed later (p. 459). For this reason the substitution reactions of aniline should not be regarded as involving any attack on the nitrogen atom, but as direct reactions with the activated carbon atom or atoms of the ring.

The influence of substituents on the basicity of the aromatic amines[1] is in general greatest in the ortho position and least in the meta. The direction of the effect depends on the nature of the group; certain groups reduce the basicity and others increase it. An approximate order in which groups can be arranged is as follows: NO_2 (strongly negative), $N:N\phi$, Br, Cl, Me, OMe (weakly positive).

Halogen derivatives. From what has been said above, it is clear that many of the halogen-substituted anilines can be obtained by direct substitution, but that those with the halogen in the meta position to the amino group are best prepared by other methods; *m*-chloraniline, for example, is prepared by the reduction of *m*-chloronitrobenzene formed in the chlorination of nitrobenzene. Aniline is sufficiently reactive to give iodo-aniline with iodine, although for the preparation of this compound it is best to treat acetanilide with iodine monochloride. The final product of the action of chlorine or bromine on aniline is the 2,4,6-tri-chloro- or -bromo-aniline, and penta-chloro- or -bromo-aniline can only be obtained by the chlorination or bromination of the 3,5-disubstituted amine. Tribromaniline is such a weak base that its salts are completely hydrolysed by water, and it is thus precipitated when bromine is added to an aqueous solution of an aniline salt. This fact serves as a sensitive qualitative test for aniline, and can be used for its quantitative estimation; the tribromaniline can be filtered off and weighed, or else by a volumetric method the solution containing aniline is treated with a known volume of a bromine solution and the excess of bromine that remains after the substitution estimated by adding potassium iodide and titrating with thiosulphate.

Sulphonic acids. The sulphonic acids derived from the aromatic amines differ very markedly in their physical properties from the other nuclear substituted amines. The reason for this is that the molecule contains both a basic and a strongly acidic group, so that the free acid is an internal salt or zwitterion, and thus in its properties it resembles a salt such as sodium chloride more closely than a typical organic compound. The best-known

[1] R. C. Farmer and F. J. Warth, *J.C.S.* 1904, **85**, 1713; N. F. Hall and· M. R. Sprinkle, *J. Amer. C. S.* 1932, **54**, 3469.

aromatic amino-sulphonic acid is aniline-*p*-sulphonic acid, usually called sulphanilic acid, and its constitution is best represented by the formula:

$$H_3\overset{+}{N}\!-\!\langle\ \rangle\!-\!SO_3^-$$
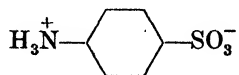
It is insoluble in alcohol, ether, and benzene, but dissolves in hot water: it blackens and decomposes at 280–300° and has no true melting-point; these properties are in marked contrast to those of both aniline and benzene sulphonic acid; the latter is extremely soluble in water, melts at 50° and can be distilled unchanged under very low pressures. Sulphanilic acid dissolves in aqueous alkalis, but is unaffected by mineral acids in spite of the fact that it contains an amino group. This behaviour is due to the great difference in the strength of the amino group as a base and of the sulphonic group as an acid; in alkaline solution the zwitterion can be converted into an anion by the following process:

$$^-O_3S \cdot C_6H_4 \cdot \overset{+}{N}H_3 + OH^- \longrightarrow \ ^-O_3S \cdot C_6H_4 \cdot NH_2 + H_2O\ ;$$
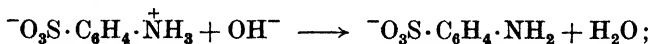
while the formation of a true kation in acid solution, which would be the process

$$H_3^+N \cdot C_6H_4 \cdot SO_3^- + H^+ \longrightarrow H_3^+N \cdot C_6H_4 \cdot SO_3H$$
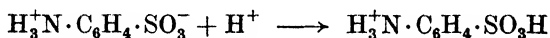
does not take place; the sulphonic ion is that of a strong electrolyte and there is no tendency for the formation of the undissociated sulphonic acid in aqueous solution. The sodium salts of sulphanilic acid can be acetylated to an N-acetyl compound, but the free acid is unattacked; this is another indication that the former contains the group —NH$_2$ and the latter does not.

Sulphanilic acid is prepared by heating aniline with excess of sulphuric acid to 180° for 4–5 hours; it is of importance in the dye-stuff industry and is obtained commercially by heating dry aniline sulphate, $\phi NH_3[SO_4H]$, best in a stream of dry air or carbon dioxide to remove the water as it is formed; this is called the baking process. It has been suggested that the first product is phenyl sulphamic acid, $\phi NH \cdot SO_3H$, which on further heating 'rearranges' to sulphanilic acid, but it is extremely doubtful whether this N-sulphonic acid can exist under the conditions used.[1] Sulphonation of aniline with fuming sulphuric acid gives a certain amount of the *m*-sulphonic acid for reasons which have been discussed above. This acid, which is called metanilic acid, is best prepared by the reduction of *m*-nitrobenzene sulphonic acid obtained by sulphonating nitrobenzene. Aniline *o*-sulphonic acid is obtained by sulphonating *p*-bromaniline, when the sulphonic group enters the ortho position to the amino group, and removing the bromine atom by reduction with zinc and alkali or with hydriodic acid. These two acids closely resemble sulphanilic acid in their properties. In the ortho and para aminosulphonic acids the sulphonic group is sometimes readily displaced by other substituents; thus sulphanilic

¹ See W. Huber, *Helv. Chim. Acta*, 1932, **15**, 1372.

acid and bromine give 2,4,6-tribromaniline,[1] and with nitric acid nitr-anilines are formed.

A very large number of sulphonic acids derived from the two naphthyl-amines are known containing up to three sulphonic groups; many of them are intermediates in the preparation of important azo dye-stuffs (see p. 449).

Nitro derivatives. The three nitranilines are yellow solids which can be recrystallized from water. *p*-Nitraniline (melting-point 147°) is best obtained by the nitration of acetanilide and removal of the acetyl group by hydrolysis; the meta compound (melting-point 114°) by the partial reduction of *m*-dinitrobenzene, and the ortho isomer (melting-point 71°), by nitrating acetanilide in acetic anhydride (see p. 12). They are all weaker bases than aniline and a mixture of the three can be separated by neutralizing their solution in acid when the ortho compound, the weakest base, is precipitated first, then the para, and finally the meta. The ortho and para compounds can also be obtained by the action of ammonia on the corresponding chloronitrobenzenes in which the halogen atom is reactive (see p. 48).

There are marked differences in the behaviour of *o*- and *p*-nitraniline on the one hand and of *m*-nitraniline on the other. The latter is unaffected by boiling with aqueous alkalis, while the former are hydrolysed to nitro-phenols and ammonia. An extreme case is 2,4,6-trinitroaniline, which is readily hydrolysed to the corresponding phenol, picric acid, and is conse-quently called picramide. Further, with sodium ethoxide in alcohol the ortho and para compounds give deep orange or red precipitates of a sodium salt of the nitraniline, while the meta compounds do not even show a change of colour.[2] The cause of these differences is indicated by the value of the electric moment of *p*-nitraniline. With the majority of *p*-di-substituted benzene compounds the electric moment is close to the vectorial sum of the moments of the two substituents, so that with *p*-nitraniline, where these moments lie in the same direction, the expected value would be the sum of the moments of aniline (1·52 D) and of nitro-benzene (3·96 D), i.e. 5·48 D. All the values found experimentally are considerably higher, their mean being 6·45.[3] Hence there must be an inter-action which increases the electric moment. Now *p*-nitraniline contains a basic group and the nitro group which is a potential anion; it might be allotted a structure (I) which is that of a zwitterion.

I.   II.
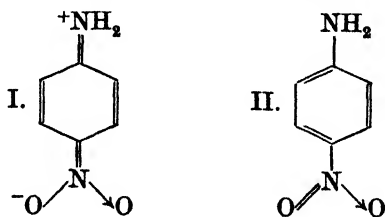
[1] J. J. Sudborough and J. V. Lakhumalani, *J.C.S.* 1917, **111**, 41.
[2] A. G. Green and F. M. Rowe, ibid. 1913, **103**, 508.
[3] K. Hojendahl, *Phys. Z.* 1929, **30**, 391; L. Tiganik, *Z. phys. Chem.* 1931, B, **14**, 135.

This is clearly not the true structure because the electric moment of (I) would be much larger than 6·5 D, and the physical properties of the compound do not r·semble those of sulphanilic acid. The structure (I), however, differs from the structure as ordinarily written (II) only in distribution of electrons, and hence there must be the possibility of resonance. *p*-Nitraniline is thus a resonance-hybrid of these two structures. It should be noticed that there is not the same possibility with sulphanilic acid because the zwitterion and the uncharged molecule differ in the position of a proton and resonance cannot take place.

The abnormal value of the electric moment of the para compound can be explained satisfactorily in this way, and the explanation can be extended to the general differences between the meta compound and the ortho and para isomers. *o*-Nitraniline can also be a resonance-hybrid of structures (III) and (IV), but *m*-nitraniline cannot, since a zwitterion would imply a structure such as (V), which would be analogous to the unknown meta-quinones.

III.   IV.

V.
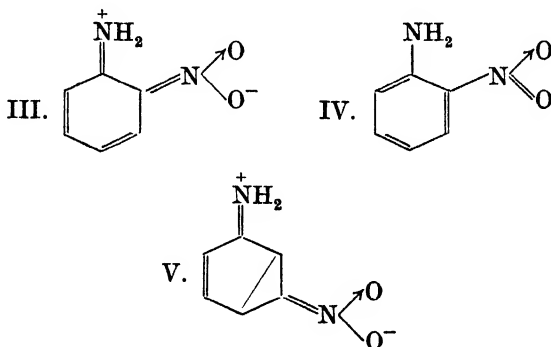
The formation of alkali salts by the ortho and para compounds is somewhat similar. The quinonoid structures shown are possible for the anions of these two compounds, but not for the meta isomer.
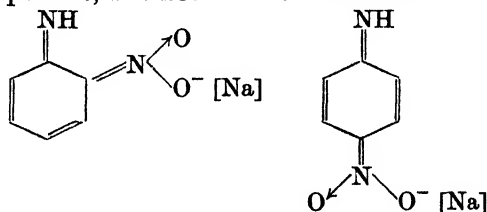
The meta compound forms no sodium salt because a quinone structure is impossible. These views as to the origin of the differences in the behaviour of the nitranilines find support in the analogous differences between the nitroso-anilines (p. 217).

Hydroxy compounds. The ortho- and para-hydroxy-anilines, usually called amino-phenols, can be prepared by reduction of the corresponding nitrophenols (see p. 47). Alternatively, the phenol is coupled with an

aromatic diazo compound, and the resulting hydroxy-azo derivative is reduced with stannous chloride.
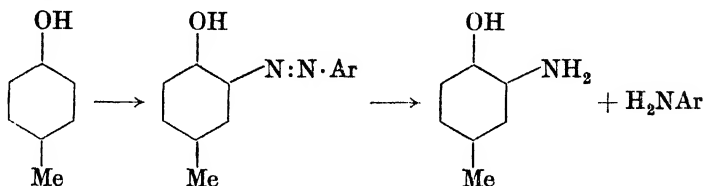
The latter method cannot be used to prepare m-amino-phenols because a phenol does not couple in the meta position. m-Amino-phenol is prepared by the reduction of m-nitro-phenol which can be obtained from m-dinitrobenzene, and also by fusing metanilic acid with caustic soda. It is prepared technically by heating resorcinol (1,3-dihydroxy-benzene) with ammonia and ammonium chloride under pressure, when one hydroxyl group is replaced by —NH$_2$: the compound is used as a component in certain azo dyes.

The amino-phenols behave both as weak acids and weak bases. They are easily oxidized, especially in alkaline solution, and thus act as mild reducing agents; for this reason certain of them are used as developers in photography. p-Amino-phenol is sold for this purpose under the name of 'rodinal' and can be prepared in one operation from nitrobenzene by electrolytic reduction in sulphuric acid, when phenylhydroxylamine, ϕNHOH, is formed and converted at once into rodinal (see p. 163).

The o-amino-phenols differ from the meta and para compounds in many reactions because of the proximity of the hydroxyl and amino groups in the molecule. They condense readily with a variety of substances to give heterocyclic compounds; examples of such reactions are shown in the following scheme:

2-Methyl-benzoxazole

2-Hydroxy-benzoxazole

Phenoxazine
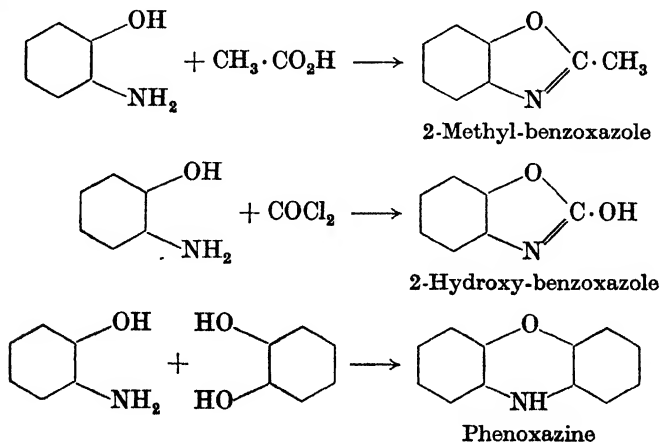
A more striking phenomenon is the ease of rearrangement in the acyl derivatives of the ortho compounds, but not in those of the meta or

para isomers. The first reaction of this type was the discovery by W. Böttcher[1] that reduction of benzoyl-o-nitrophenol gives a product which is soluble in aqu⌐ous alkali and hence must contain a free hydroxyl group:
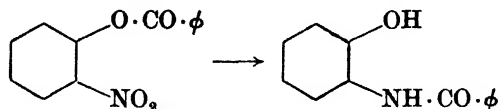
the O-benzoyl-amino-phenol has rearranged during the reduction to an N-benzoyl compound. The best investigated case is that of o-amino-phenyl ethyl carbonate.[2] This compound, which contains an acyl group attached to oxygen, can be obtained by reducing the corresponding nitro compound at 0°; it is basic and insoluble in aqueous alkali. As its hydrochloride it is completely stable, but the free base changes spontaneously in the course of a few hours into o-hydroxy-phenyl-urethane, which is not basic and is soluble in alkali.
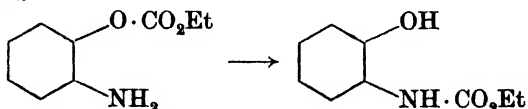
If the hydrochloride of the base is dissolved in water, the urethane gradually separates, and measurement of the rate of isomeric change shows that it is directly proportional to the concentration of free base formed by hydrolysis of the salt.[3] There is little doubt that changes of this type are true intramolecular rearrangements which can occur because of the proximity of the hydroxyl and amino groups: they are analogous to the intramolecular rearrangements of imino-ethers and amidines which are discussed later (pp. 154 and 156).

More complicated examples of migration in o-amino-phenols are known. Migration of an acyl group can take place during acylation; the same product is formed both by the benzoylation of 4-bromo-6-acetamino-o-cresol, and the acetylation of the corresponding 6-benzoylamino compound.[4]
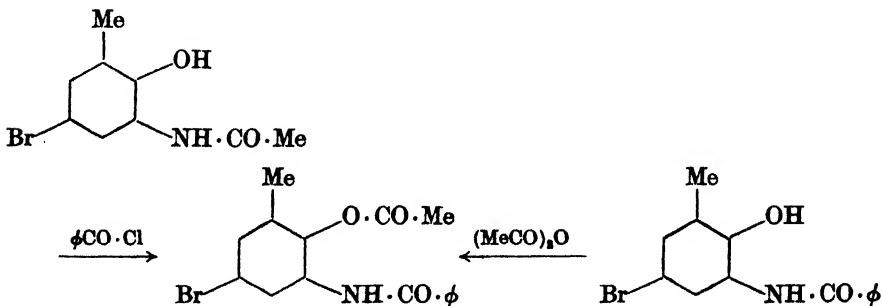
[1] *Ber.* 1883, **16**, 629.
[2] J. H. Ransom, *Amer. Chem. J.* 1900, **23**, 1; *Ber.* 1900, **33**, 199.
[3] J. Stieglitz and H. T. Upson, *Amer. Chem. J.* 1904, **31**, 458.
[4] L. C. Raiford and J. R. Couture, *J. Amer. C. S.* 1922, **44**, 1792.

Similar rearrangements occur also in the acyl derivatives of o-hydroxy-benzylamine (VI), but not in the meta and para compounds, and in the phenylhydrazone of salicyl-aldehyde (VII). They have never been observed, however, in the derivatives of o-amino-benzyl alcohol (VIII) whose O-acyl compounds are quite stable.

VI.

VII.

VIII.
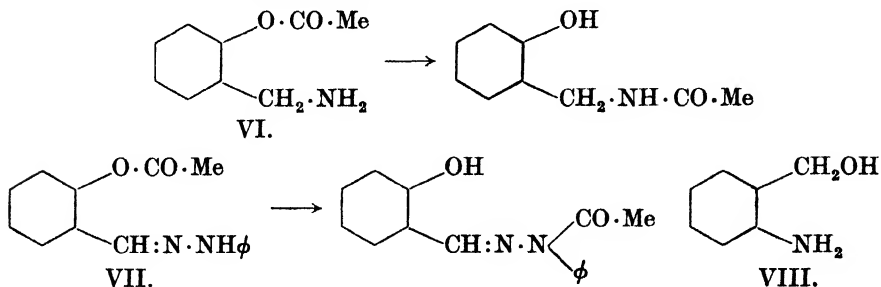
Homologues of Aniline.

The physical properties of the homologues of aniline have been described already (p. 49). Their chemical behaviour is, in general, that of aniline except in so far as the side chains interfere; thus p-acetotoluidide on nitration cannot give a p-nitro compound, and the ortho compound is formed.
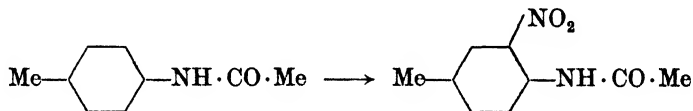
An alkyl group attached to the nucleus is, however, sometimes eliminated when a quinone is formed on oxidation; for example, mesidine gives m-xyloquinone:
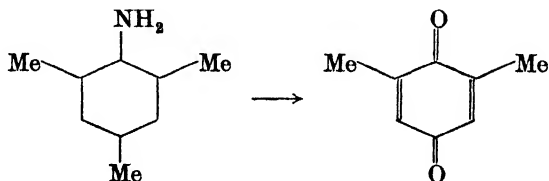
The homologues of aniline can be prepared by obvious modifications of the general methods of obtaining primary aromatic amines; those which contain alkyl groups in the para and ortho positions are also formed in a curious reaction, often called the Hofmann-Martius rearrangement. This in essence is the transference of the alkyl group of an N-alkyl aniline from the nitrogen atom to the ring; the p-alkyl aniline is formed if the para position is free, and if not, an o-alkyl aniline can be formed, but the meta position is seldom occupied.[1] By this method Hofmann prepared penta-methyl-aniline by introducing three methyl groups into 3,5-dimethyl-aniline. The N-alkyl anilines themselves are quite stable to heat, since they can be prepared by passing a mixture of aniline and an aliphatic

[1] D. H. Hey, *J.C.S.* 1931, 1581.

alcohol over alumina or thoria at 400–450°,[1] but when their hydrochlorides or hydrobromides are heated in a sealed tube to temperatures above 250°, the apparent migration of the alkyl group to the ring takes place. Methylaniline hydrochloride gives a good yield of the hydrochloride of p-toluidine. A similar reaction is also brought about by mixing the free amine with the dry chloride or bromide of zinc, cobalt, or cadmium, and heating to 250–300°.[2] The mechanism of this apparent migration has been the subject of much discussion, and several conflicting views have been advanced. The main point at issue is whether the reaction is a true rearrangement in which only one molecule is involved, or, as with some other apparent migrations, a more complex reaction which proceeds by dissociation of the molecule into fragments which recombine to the final product. The difficulty of settling this point arises from several causes; the reaction takes place at a high temperature and in a heterogeneous system so that measurement of its rate is impossible; the product of the reaction is not a unique substance but a mixture of several and it is difficult to say whether some of the compounds obtained are merely formed in side reactions or are essential intermediate products in the main reaction. A further complication appears in the rearrangements in the alkyl group itself which occur in some cases.

On general grounds a purely intramolecular rearrangement seems unlikely. If the alkyl group migrated preferentially to the ortho position, such a mechanism would be indicated, but the main product is the p-alkyl compound; the distance between the nitrogen and p-carbon atoms is so great and distortion of the rigid benzene ring seems so unlikely that it is not easy to see how intramolecular rearrangement could occur. For this reason dissociation of the amine salt into two compounds which interact in a bimolecular reaction seems a more plausible hypothesis. A. Michael in 1881[3] suggested that the first step was the formation of the alkyl halide which later reacted with the aniline formed.

$$\phi \cdot \mathrm{NMeH_2[Cl]} \longrightarrow \phi\mathrm{NH_2} + \mathrm{MeCl}$$

$$\mathrm{MeCl} + \langle\bigcirc\rangle\mathrm{NH_2} \longrightarrow \mathrm{Me}{-}\langle\bigcirc\rangle{-}\mathrm{NH_3[Cl]}$$
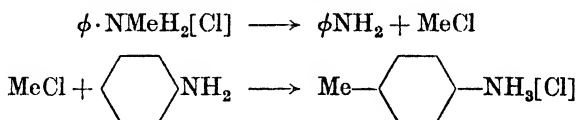
If this is true, a certain amount of dimethylaniline would be expected since the methyl chloride might react not with the aniline, but with unchanged methylaniline as in a normal Hofmann amine synthesis:

$$\phi\mathrm{NMeH} + \mathrm{MeCl} \longrightarrow \phi\mathrm{NMe_2H[Cl]}.$$

This prediction is fulfilled, since E. Beckmann and E. Correns[4] found dimethylaniline among the products. Again the alkyl halides are volatile, and if they are actually formed, there might be considerable loss when the reaction is carried out not in a sealed tube, but in an open vessel. The

[1] A. Mailhe and F. de Godon, *C.r.* 1918, **166**, 467.
[2] J. Reilly and W. J. Hickinbottom, *J.C.S.* 1920, **117**, 107.
[3] *Ber.* **14**, 2107, footnote.   [4] Ibid. 1922, **55**, 852.

experimental results confirm this prediction.[1] When ethylaniline hydrochloride is heated in a long vertical open tube, much aniline is formed; butylaniline hydrochloride also gave a little aniline and a certain amount of *p*-butyl-aniline.

An alternative view is that the dissociation product is not the alkyl halide, but an ethylene which is sometimes found in quantity among the products. Hickinbottom[2] showed that isoamyl-aniline hydrobromide gave a considerable amount of amylene and aniline together with 35 per cent. of *p-tert.*-amyl aniline; the latter is the 'migration' product and at some stage in its formation the isoamyl group has been converted into a tertiary amyl group. Hence another possibility is the following:

$$NH \cdot CH_2 \cdot CH_2 \cdot CHMe_2 \qquad NH_2 \qquad\qquad NH_2$$

$$\longrightarrow \quad + CH_3CH:CMe_2 \longrightarrow$$

$$CH_3 \cdot CH_2 \cdot CMe_2$$
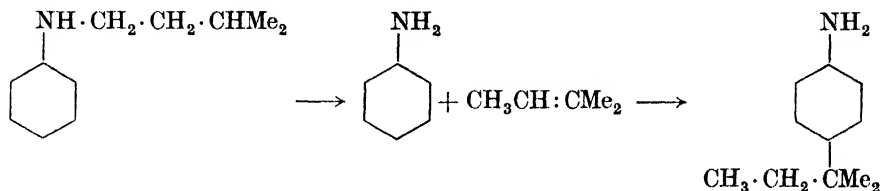
Study of the reaction which takes place with the free amine and a metallic salt leads to further complications; in the first place the formation of free aniline which is to be expected in an open vessel through loss of a volatile intermediate does not take place,[3] and secondly groups such as isoamyl and isobutyl migrate without being transformed into the corresponding tertiary groups, although this transformation is usual with the hydrochlorides.[4] There is consequently the possibility that the mechanism of the reaction is not always the same. The evidence is clearly insufficient to decide what is the actual course of the reaction.

Aromatic Diamines.

Compounds containing two primary amino groups attached to a benzene ring can be prepared by the reduction of dinitro compounds and nitro-anilines, usually with tin or stannous chloride and hydrochloric acid. Another convenient method for obtaining *p*- and *o*-diamines is to couple an aromatic amine with an aromatic diazo compound (p. 445), and reduce the resulting amino-azo compound:

$$H_2N- \longrightarrow H_2N- -N:N \cdot Ar \longrightarrow H_2N- -NH_2 + H_2NAr.$$

$$Me \qquad\qquad Me \qquad\qquad\qquad Me$$
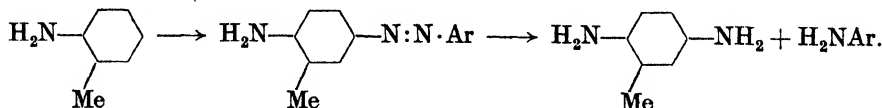
The three simple diamines derived from benzene are crystalline solids which are colourless when pure but turn brown on standing in air; they are much more soluble in water than aniline and its homologues, and can be distilled without decomposition. They are diacidic bases and form

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[1] W. J. Hickinbottom, *J.C.S.* 1927, 64.   [2] Ibid. 1932, 2396.

[3] Hickinbottom and A. C. Waine, ibid. 1930, 1558.

[4] Hickinbottom and G. H. Preston, ibid. 1932, 1566.

salts with two equivalents of mineral acid; they are easily oxidized, especially in aqueous solution, but the crystalline salts are stable.

The three isomers differ markedly in their chemical behaviour, which is largely determined by the relative position of the two amino groups.

The ortho diamines readily undergo ring closures to form heterocyclic compounds. Only a few examples will be mentioned. The amino groups cannot be diazotized under normal conditions, because ring closure takes place and a benztriazole (azimido- or azimino- compound) is formed.
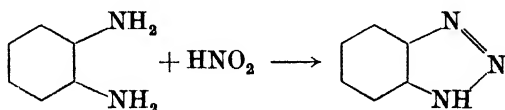
The benztriazoles are extremely stable compounds with very weak basic and acidic properties.

Diamines react with acid anhydrides to give di-acyl derivatives; when the two amino groups are in the ortho position to one another, this compound readily loses a molecule of the acid on heating, and a benziminazole is formed:
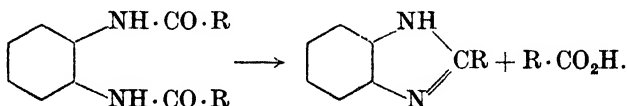
The same product is formed by boiling the o-diamine with the anhydrous acid, or its amide or ester. The benziminazoles contain a glyoxaline ring condensed with a benzene ring and are fairly strong bases in marked distinction to the true amides such as $C_6H_4(NH \cdot COMe)_2$ formed from meta and para diamines. o-Diamines condense very readily with α-diketones to give quinoxalines, which are sometimes called azines, a name which should be avoided because it is also applied to a group of hydrazine derivatives of entirely different constitution (see p. 393).
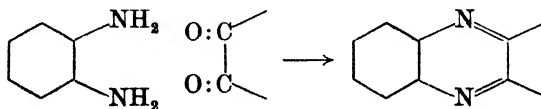
This reaction can be used to detect the presence of an o-diamine; a solution in acetic acid is boiled with phenanthraquinone, when the very sparingly soluble phenanthraphenazine separates.
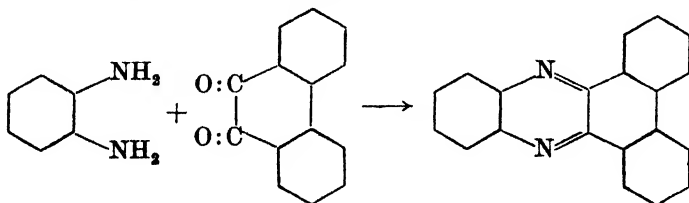
Some of the oxidation products of o-phenylene diamine have a similar

constitution. If its solution in hydrochloric acid is warmed with ferric chloride, long deep red needles of diamino-phenazine crystallize out:

$$\text{(o-diamine)} + \text{(o-diamine)} + 3O \longrightarrow \text{(diamino-phenazine)} + 3H_2O.$$
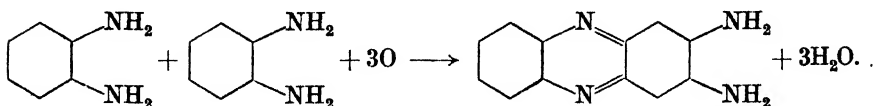
The meta-diamines are incapable of these ring closures, but show a very characteristic reaction with nitrous acid. In strong hydrochloric acid with nitrous acid always in excess both amino groups of *m*-phenylene diamine are diazotized, but with the usual conditions of diazotization a brown dye of the amino-azo class is obtained. This is a mixture of compounds formed by the coupling of the diazotized base with unchanged diamine; its principal constituents are the mono-azo and disazo compounds shown.

$$\text{(C}_6\text{H}_3(\text{NH}_2)\text{N}_2\text{Cl)} + \text{(C}_6\text{H}_4\text{NH}_2\cdot\text{NH}_2) \longrightarrow -N{=}N{-} \longrightarrow -N{=}N{-}$$
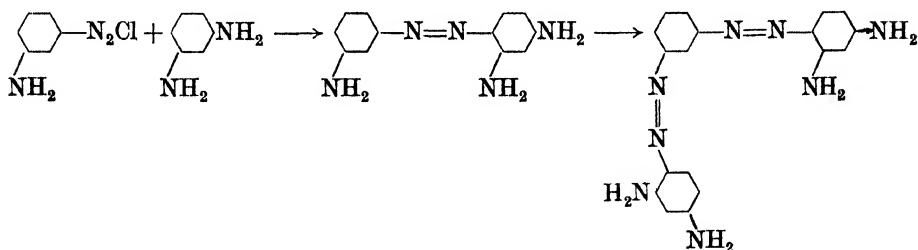
This is called Bismarck brown or Manchester brown, the earliest azo dye (1866). The reaction can be used as a sensitive test for the detection and colorimetric estimation of nitrous acid.

The para-diamines are diazotized in a normal manner. They are distinguished from the other two classes by their oxidation products. With many oxidizing agents they give quinones.

$$\text{(p-phenylenediamine)} \longrightarrow \text{(quinone)}$$
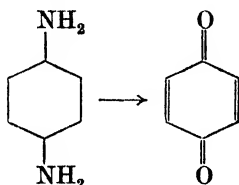
Intermediate stages in this oxidation, quinone diimines and Würster salts, are described later (p. 97).

Para-diamines are intermediate products in the preparation of several classes of dye-stuffs and are usually formed in the reaction mixture in which the dye is prepared by reduction of a nitroaniline or a nitrosodialkyl-aniline.

Polyamines. Of the three possible triamino-benzenes the best known is the symmetrical (1,3,5) compound which can be obtained by the reduction

of the corresponding nitro compound. The hydrochloride of this triamine is hydrolysed in boiling water to phloroglucinol:

$$
\text{NH}_3[\text{Cl}] \qquad\qquad \text{OH}
$$

[Cl]H_3N — $\text{NH}_3[\text{Cl}]$ $\longrightarrow$ HO — OH $+ 3\text{NH}_4\text{Cl}.$
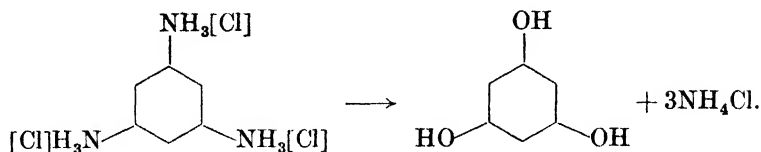
Since 1,3,5-trinitrobenzene can be obtained from trinitrotoluene by oxidation to trinitrobenzoic acid and loss of carbon dioxide, this forms the best method for preparing phloroglucinol.[1]

The tri-, tetra-, and penta-amino-benzenes are progressively less stable and more readily oxidized. The penta- and hexa-amino compounds are difficult to obtain because during the reduction of a polynitro compound by most reagents, one or more amino groups are lost as ammonia. The best reducing agent for the final stage is phenylhydrazine at 120–140°.[2] Penta-amino-benzene can be prepared by nitrating m-nitraniline to tetranitroaniline, reducing this to trinitrodiamino-benzene with stannous chloride and reducing the remaining nitro groups with phenylhydrazine. It is insoluble in all organic solvents except phenylhydrazine; its aqueous solution decomposes almost instantaneously.

The hexa-amino compound is much more stable; it is prepared from 1,3,5-trinitrobenzene through the stages 3,5-dinitroaniline, pentanitroaniline, 2,4,6-trinitro-1,3,5-triamino-benzene which is reduced with phenylhydrazine. It melts with decomposition at 247–248° and is fairly soluble in water and phenylhydrazine, but in no other solvent; in aqueous solution it decomposes in about 24 hours. It forms a hexa-acetyl derivative, and its most stable salt is the tetrahydrochloride.

Amino-Di- and Triphenylmethanes

The amines derived from the hydrocarbons diphenylmethane and triphenylmethane are closely related to di-and triphenylmethane dye-stuffs. As has been mentioned already, a member of this group was one of the first synthetic dyes to be discovered and manufactured. These dyes give very brilliant clear colours on fabrics, but are not fast to acids, alkalis, or light, and, in consequence, they have been displaced to a large extent by more stable compounds. It was the lack of fastness of these dyes that gave rise to the old-fashioned belief that 'aniline-dyes' were universally inferior to natural dye-stuffs, a belief which the extraordinary fastness of dyes such as those of the anthraquinone and indanthrene groups has disproved. In spite of their diminished technical importance, a detailed description of these dyes is necessary because they present one of the simplest examples of compounds with true dye-stuff properties, and the discussion of their structure, which has continued with hardly any break

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[1] *Organic Syntheses*, **9**, 74.
[2] B. Flürscheim and E. L. Holmes, *J.C.S.* 1929, 330.

ever since their composition was established, is of fundamental importance in the question of the constitution of deeply coloured organic compounds in general.

First of all a simple account will be given of the properties and behaviour of some of the amines derived from triphenylmethane and their related dye-stuffs. Compounds with one, two, and three amino groups in the para positions of the aromatic nuclei can be obtained by various reactions, e.g. by reduction of the corresponding nitro compounds. They are colourless crystalline solids and form colourless salts.

m.p. = 84°	140°	208°
I.	II.	III.
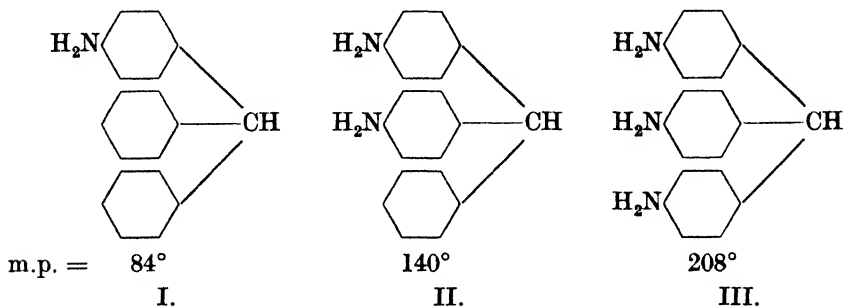
The characteristic behaviour of the salts of all these amines is that they are oxidized by practically all oxidizing agents to give coloured compounds, which are also salts. That derived from the mono-amine has a weak orange colour, but those from the diamine (II) and the triamine (III) are intensely coloured dye-stuffs: the hydrochloride of the diamine gives the dye Doebner's violet and that of the triamine gives pararosaniline which is also known as parafuchsine.[1] The coloured salts can be reduced back again to the colourless salts of the amino-triphenylmethanes: the latter are described as the leuco-bases of the dye-stuffs. There is a definite distinction, however, between the oxidation products obtained from (I) on the one hand and from (II) and (III) on the other: the former is coloured, but the depth of colour is too weak for its use as a dye, while the two latter are true dye-stuffs. Similar phenomena are observed with the N-alkyl derivatives of all the three amines; replacement of some or all of the amino hydrogen atoms by methyl or ethyl groups alters the colour of the oxidation product, but does not essentially change the general behaviour. The dimethyl derivative of (I) gives an orange-red compound of little depth of colour, the tetramethyl derivative of (II) gives the well-known dye malachite green, and the hexamethyl derivative of (III) gives crystal violet. If instead of the p-amino compounds we consider those in which the amino group is in the meta position, none of these phenomena are observed; the meta amines are bases, but they do not give coloured salts on gentle oxidation. In the ortho series the facts are

---

[1] The prefix para has nothing to do with the position of substituents: it was introduced years before the structure of benzene was known to distinguish this dye from a similar one which was called rosaniline or fuchsine.

less clear; there are indications of dye-stuff formation but it does not take place so readily as in the para compounds.

The dye-stuffs obtained in the para series are strong electrolytes and are soluble in water. If caustic soda is added to their solution, the colour fades, not instantaneously but at a measurable rate, and a colourless solid separates from the solution. Analysis shows this compound to be a hydroxy derivative of the leuco-base; it is an alcohol and not a phenol and is easily reduced to the leuco-base. These alcohols are described as the carbinol bases of the dye-stuffs and their constitution is shown in formulae (IV) and (V).

$$
\begin{array}{cc}
\text{H}_2\text{N}\!\!-\!\!\bigcirc & \text{H}_2\text{N}\!\!-\!\!\bigcirc \\
\text{H}_2\text{N}\!\!-\!\!\bigcirc\!\!-\!\!\text{C}\cdot\text{OH} & \text{H}_2\text{N}\!\!-\!\!\bigcirc\!\!-\!\!\text{C}\cdot\text{OH} \\
\bigcirc & \text{H}_2\text{N}\!\!-\!\!\bigcirc \\
\text{IV.} & \text{V.}
\end{array}
$$
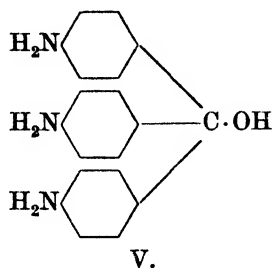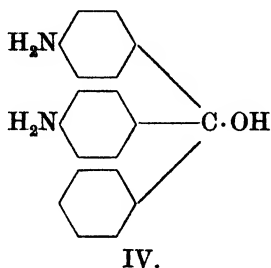
The carbinol bases are converted back into the dyes by acids and the composition of the dye shows that in this change the hydroxyl group of the carbinol is replaced by the acid anion. Thus the composition of pararosaniline (from V) is given by the formula $(\text{H}_2\text{N}\cdot\text{C}_6\text{H}_4)_3\text{CCl}$, but the chlorine atom is an ion and the compound is a salt. The relation between carbinol-base and dye differs from that between a true base and its salt: in this latter case salt formation from the base is instantaneous and the base is itself an electrolyte, while the carbinol-bases only form the dyes slowly (sometimes heating is necessary), and they are not electrolytes. The carbinol-bases belong to the class of pseudo-bases, other examples of which are described in later chapters of this book (pp. 524 and 549). Another series of derivatives can be obtained from those dyes in which at least one amino group contains a hydrogen atom; these are the so-called Homolka bases and are obtained by extracting with ether an aqueous solution of the dye immediately after it has been made alkaline. They are somewhat unstable yellow solids and their composition corresponds to that of the carbinol-base less one molecule of water, and they are converted back into the dye by acids, the molecule of acid being added on. They can thus be described as anhydro-bases, and are formed either by removal of the acid radical and an amino hydrogen atom from the dye, or by removal of the hydroxyl group and an amino hydrogen atom from the carbinol.

The colour of the dyes is also changed if excess of a mineral acid is added to their solutions. A diamino dye such as malachite green (see Table below) slowly loses its colour and gives a yellow solution. A triamino dye such as methyl violet first becomes green and then yellow on further

addition of acid. Dilution with water, i.e. lowering of the hydrogen ion concentration, reverses these colour changes.

The formulae of the carbinol-bases of some well-known dyes of the diamino and triamino series are as follows:


Carbinol-base of Doebner's violet.

Carbinol-base of malachite green.

Carbinol-base of patent blue A.

Carbinol-base of pararosaniline.

Carbinol-base of methyl violet.

Me$_2$N⟨⟩

Me$_2$N⟨⟩——C·OH   Carbinol-base of crystal violet.

Me$_2$N⟨⟩

Me

ϕNH⟨⟩

ϕNH⟨⟩—·—·—C·OH   Carbinol-base of spirit-soluble aniline blue.

ϕNH⟨⟩
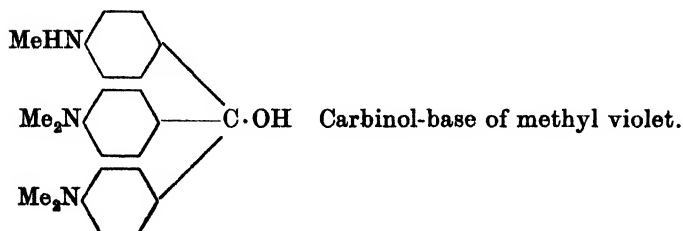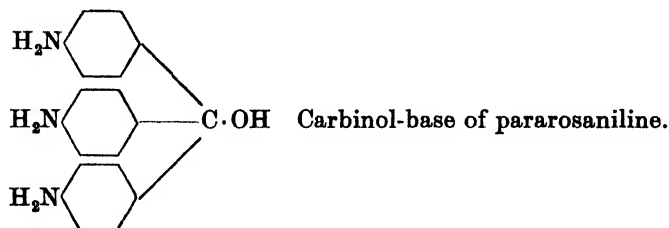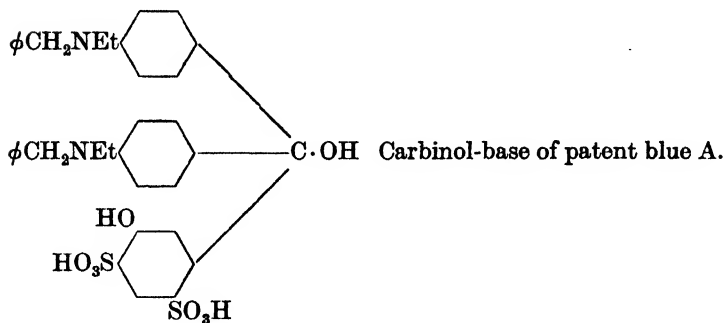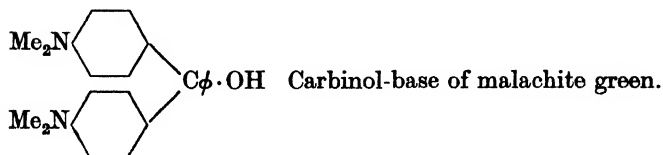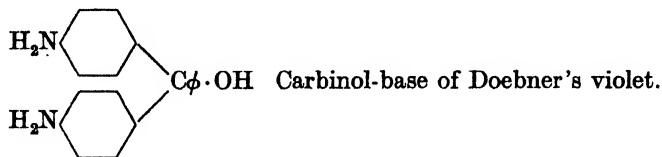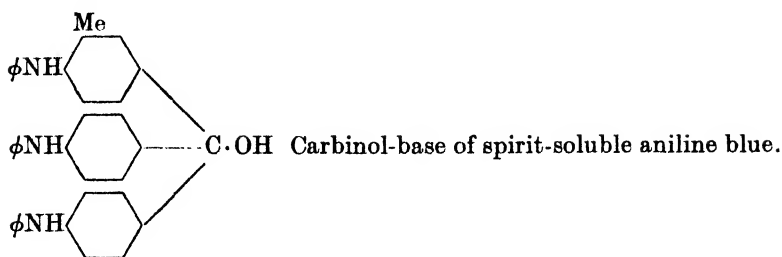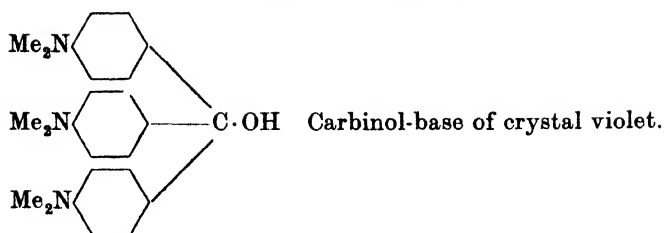
Before discussing the constitution of the dyes a short account will be given of their methods of preparation. The discovery of the first member of the group has been mentioned above (p. 53): Verguin, a teacher at the Collège de Lyon, found that oxidation of a mixture of aniline and its homologues with stannic chloride gave the dye which is called rosaniline or fuchsine. His product was a mixture of several compounds, because his aniline contained o- and p-toluidine; its main constituent was formed by the condensation of one molecule of aniline with one of o-toluidine and one of p-toluidine, followed by oxidation of the leuco-base in the presence of hydrogen chloride to give the dye; this is rosaniline or fuchsine in the strict sense.

H$_2$N⟨⟩

H$_2$N⟨⟩   + H$_3$C—⟨⟩NH$_2$ ——→

Me

H$_2$N⟨⟩

H$_2$N⟨⟩ ⟩CH—⟨⟩NH$_2$

Me
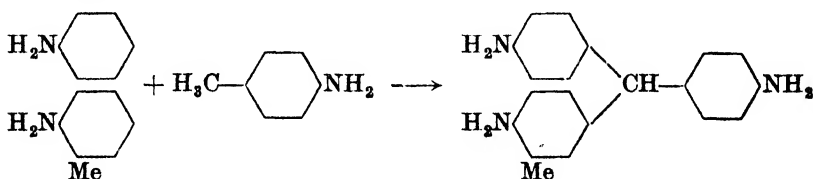
Oxidation of a mixture of aniline and p-toluidine similarly gives pararos-aniline, but the yield of dye is smaller, so that rosaniline is usually made rather than pararosaniline. The mixed amines are heated with an oxidizing agent to 180–190°, the resulting mass is dissolved in water and the dye caused to crystallize as a chloride by addition of salt. Many oxidizing agents can be used; those of technical importance are arsenic acid and nitrobenzene. The former gives a clean product but it contains a small amount of arsenic which is objectionable because of its poisonous nature. In these methods the methane carbon atom is provided by a methyl side chain in toluidine or xylidene, but triphenylmethane dyes are formed with surprising ease and a side chain is not necessary. A variety of com-

pounds, such as carbon tetrachloride, oxalic acid, or chloropicrin, will enter into the reaction and provide the necessary carbon atom. A carbon atom can even be split off from a dimethylamino group for this purpose; if dimethylaniline is heated with a copper salt and a little water, together with some phenol as catalyst and much solid sodium chloride to increase the surface, it is oxidized by the air to methyl violet.

The second general method, discovered by E. and O. Fischer, is to condense an aromatic aldehyde with two molecules of a tertiary base. Zinc chloride was the condensing agent originally used, but it has been replaced by sulphuric acid. The product is necessarily a diamino-triphenyl-methane derivative and is the leuco-base: it is converted into the dye by oxidation in acid solution, usually with lead peroxide. An important example is the preparation of malachite green from benzaldehyde and dimethylaniline:

$$2\,Me_2N\!\!\left\langle\;\;\right\rangle + OCH\phi \;\longrightarrow\; \left(Me_2N\!\!\left\langle\;\;\right\rangle\!\!-\right)_2 CH\phi.$$
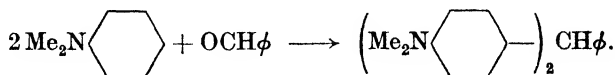
If benzaldehyde is replaced by benzotrichloride, ϕCCl_3, the dye is formed in one stage.

The last method of preparation that will be mentioned involves Michler's ketone or Michler's hydrol. The ketone is made by the action of phosgene on dimethylaniline and can be reduced to the hydrol:

$$2\,Me_2N\!\!\left\langle\;\;\right\rangle + COCl_2 \longrightarrow \left(Me_2N\!\!\left\langle\;\;\right\rangle\!\!-\right)_2 CO \longrightarrow \left(Me_2N\!\!\left\langle\;\;\right\rangle\!\!-\right)_2 CHOH.$$
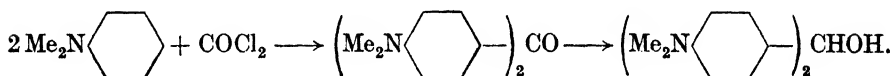
Michler's hydrol condenses with dimethylaniline to give the leuco-base of crystal violet,

$$\left(Me_2N\!\!\left\langle\;\;\right\rangle\!\!-\right)_2 CHOH + \left\langle\;\;\right\rangle NMe_2 \longrightarrow \left(Me_2N\!\!\left\langle\;\;\right\rangle\!\!-\right)_3 CH,$$
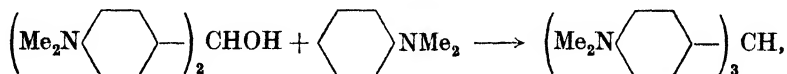
and the ketone condenses with dimethylaniline in presence of phosphorus trichloride or oxychloride to give crystal violet itself.

$$\left(Me_2N\!\!\left\langle\;\;\right\rangle\!\!-\right)_2 CO + \left\langle\;\;\right\rangle NMe_2 \longrightarrow \left(Me_2N\!\!\left\langle\;\;\right\rangle\!\!-\right)_3 COH \longrightarrow dye.$$
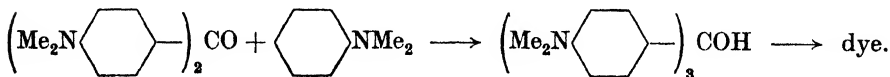
Crystal violet can be manufactured in one operation by passing phosgene into dimethylaniline and some zinc chloride until two-thirds of the amine have been converted into the ketone; the mixture is then heated to bring about the condensation to the dye.

Many of the dyes derived from amino-triphenylmethanes were being manufactured on the commercial scale long before there was any knowledge of the elements of their constitution or, indeed, of the true constitution of benzene. That they are, in fact, derivatives of the p-amino-triphenylmethanes was established during the period 1870–80 by the work

of Hofmann, Rosenstiehl, Graebe, and Caro, and especially by the facts discovered by Emil Fischer working in collaboration with his cousin Otto Fischer.[1] The more important pieces of evidence are as follows:

(i) Rosaniline and pararosaniline and their leuco-bases can be diazotized, and on warming the solution of the diazo compound a trihydroxy compound is formed. This shows that the molecule contains three primary amino groups attached to aromatic nuclei.

(ii) If the leuco-bases of rosaniline and pararosaniline are diazotized in alcohol, the amino groups are eliminated in the normal way and hydrocarbons are formed. That from rosaniline was an unknown hydrocarbon, $C_{20}H_{18}$, but that from pararosaniline was triphenylmethane, a known compound which had been prepared by Kekulé and Franchimont in 1872. The $C_{20}H_{18}$ hydrocarbon was shown to be a tolyl-diphenylmethane and rosaniline was thus proved to differ from pararosaniline by a methyl group attached to one of the aromatic nuclei. Hence the leuco-bases of these dyes are triamino-triphenylmethanes and since they are prepared from amines in which there is only one amino group attached to each aromatic nucleus, it seemed almost certain that each of the phenyl groups carries one amino group. This view of the structure of the leuco-bases is supported by the fact that nitration of triphenylmethane gives a trinitro compound which can be reduced to a triamine identical with the leuco-base of pararosaniline.

(iii) The position of the amino groups in the rings is the only point that remains. It is probably the same for all three and is probably para, because although p-toluidine and aniline give pararosaniline on oxidation, o-toluidine and aniline give no dye-stuff at all. Further the trihydroxy compound obtained by diazotization of rosaniline, which is a substance called aurin, gives on oxidation p-hydroxybenzoic acid. The position of the amino groups was finally proved by the following facts: benzaldehyde and aniline condense to give a diamino-triphenylmethane which by diazotization and treatment with alkali is converted into dihydroxybenzophenone, a compound in which both hydroxyl groups are known to be in the para position because the compound can be obtained from anisaldehyde, a known p-methoxy compound. Further, p-nitrobenzaldehyde condenses with aniline to give a nitro diamino-triphenylmethane derivative which is reduced to the leuco-base of pararosaniline. Hence all the amino groups are in the para position.
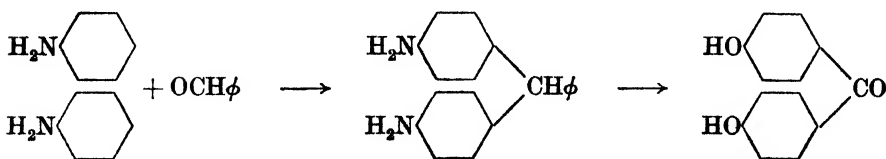
$\longrightarrow$ leuco-pararosaniline.
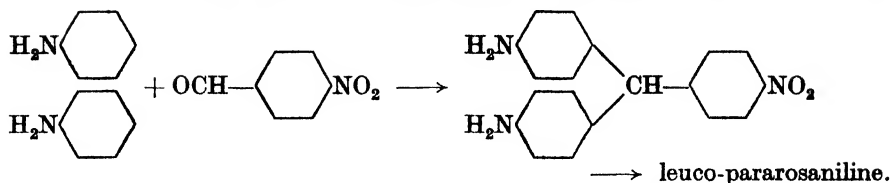
The position of the extra methyl group in rosaniline follows from the fact that, in order to obtain rosaniline, *o*-toluidine must be present. Hence the methyl group is in the ortho position to the amino group of one nucleus. This was confirmed by condensing 4-nitro-3-methylbenzaldehyde with aniline: reduction of the product gave the leuco-base of rosaniline.

The structures of the leuco-bases and carbinol-bases of the amino-triphenylmethane dyes have been established beyond doubt, but there remains the much more complicated question of the structure of the dyes themselves. If the carbinol-base of one of these dyes is treated with hydrochloric acid, a colourless substance is transformed at a measurable rate into a coloured one, and the intensity of the colour is far greater than that of many other classes of organic compounds which are described as coloured. This can be illustrated by the fact that a $N/50,000$ solution of malachite green has about the same depth of colour as a $N/1$ solution of copper sulphate, while a $N/50$ solution of quinone has about the same as that of $N/1$ potassium chromate solution. What is the structure of the dye-stuff and what is the origin of its intense absorption?

Analysis shows that when the carbinol-base is converted into the dye, it loses a hydroxyl group and gains a chlorine atom. Rosenstiehl assumed that there was direct replacement and wrote the formula of pararosaniline as in (I). E. and O. Fischer suggested that a molecule of hydrogen chloride
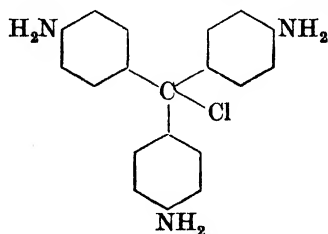
I.
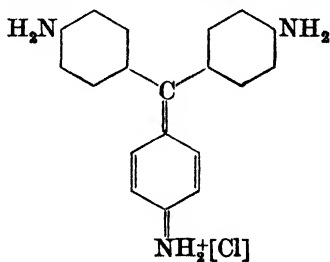
II.
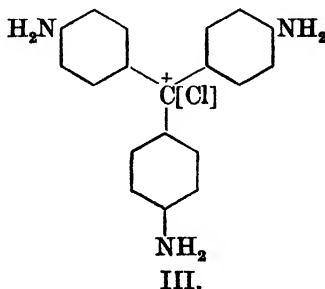
III.

formed a salt with one amino group and then water was lost to give a quinone. They used for the quinone a structure which is now known to be wrong, but Nietzki emended this and proposed the formula (II), in which one ring has a structure similar to that in ordinary benzoquinone. Discussion of the structure of the dyes was for some years a discussion of the relative merits of these two formulae and this closed in favour of the second or quinonoid structure. Much later, when the properties of trivalent carbon compounds became known, the merits of an amended version of the first formula were advocated and the controversy reopened. The most satisfactory representation of the structure is, however, an amendment or extension of the quinonoid formula.

Structure (I), as it stands, offers hardly any explanation for the characteristic behaviour of the dye-stuffs. Compounds of this structure are known: there is the carbinol-base in which a hydroxyl group is attached to the methane carbon atom in place of the chlorine atom, the cyanide $Ar_3C \cdot CN$ which is formed by the action of aqueous potassium cyanide on the dye,[1] and the acid and its ester, $Ar_3C \cdot CO_2Et$, which can be prepared in various ways, e.g. by the action of aluminium chloride on a mixture of oxalic ester and dimethylaniline:

$$3\,Me_2N\!\!\left\langle\;\bigcirc\;\right\rangle + EtO_2C \cdot CO_2Et \;\longrightarrow\; \left(Me_2N\!\!\left\langle\;\bigcirc\;\right\rangle\!\!-\right)_{3} C \cdot CO_2Et.$$
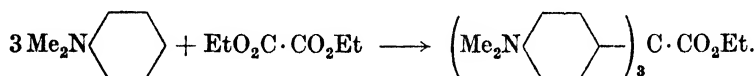
All these compounds are colourless substances soluble in organic solvents and insoluble in water. The dyes are essentially intensely coloured salts, soluble in water and not in benzene.

On the other hand many facts can be advanced as evidence for formula (II). It is the formula of a salt and it gives some explanation of the phenomena observed when the equivalent of caustic alkali is added to a solution of the dye.[2] At first the conductivity of the solution is the sum of those of the dye-salt and alkali separately and the colour is unchanged. The solution must contain the ions of a highly dissociated coloured hydroxide. On standing, and more rapidly on warming, the conductivity falls and the colour diminishes, until, after some hours in the cold, the solution is colourless and its conductivity is that of the alkali chloride it contains. The rate of the change can be followed by measurement of conductivity or of colour,[3] and is found to be proportional to the concentra-

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[1] The formation of the cyanide from the dye is parallel with that of the carbinol-base. Hydrocyanic acid, like water, is a very weak acid and its anion, CN^-, like that of water, OH^-, is often more stable when covalently linked than as an ion. Just as in pseudo-base formation the true base, an electrolyte, changes into a non-electrolyte, so the cyanides of certain bases have only a temporary existence as salts and change into compounds of structure analogous to that of the pseudo-base (examples will be found on p. 553).

[2] A. Hantzsch and G. Osswald, *Ber.* 1900, **33**, 278.

[3] P. Gerlinger, ibid. 1904, **37**, 3958; N. V. Sidgwick and T. S. Moore, *Z. phys. Chem.* 1907, **58**, 385; *J.C.S.* 1909, **95**, 889; Sidgwick and A. C. D. Rivett, ibid. 899.

tion of the kations of the base and the hydroxyl ions. Nietzki's formula will cover these facts; the dissociated coloured hydroxide is the ammonium hydroxide corresponding to the salt (II) and this can change irreversibly into the colourless undissociated carbinol-base just as in many other cases of pseudo-base formation (e.g. p. 549).

Structure (II) will also account for the Homolka bases which, as described above, are obtained by adding excess of alkali to a solution of a dye and extracting at once with ether. They are only formed from those dyes in which there is at least one hydrogen atom attached to nitrogen, and hence they can satisfactorily be allotted formula (IV). Such a formula

IV.

V.

VI.
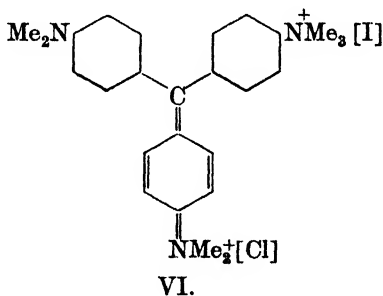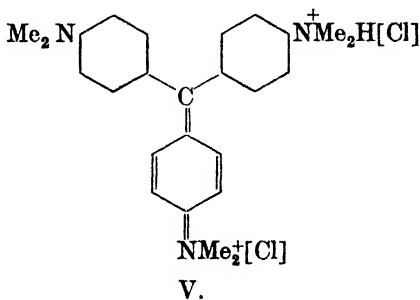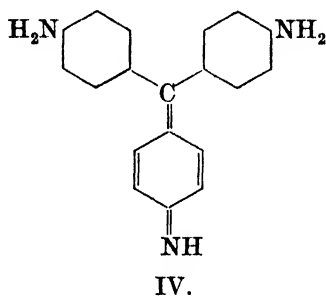
also accounts for their behaviour to acids, when the dye is regenerated, and their instability in aqueous solution when they are converted into the carbinol; the former is simply the addition of a proton àt the imino group to give the kation of (II), and the latter the addition of water to the quinonoid system. The Homolka bases are anhydro-bases formed by loss of water from the ammonium hydroxide, and their relation to those hydroxides recalls that of ammonia to ammonium hydroxide or of the methylene-bases of certain quinolinium hydroxides to those hydroxides (see p. 556).

A further powerful argument in favour of Nietzki's formula is the fact that the meta amines of triphenylmethane do not give rise to dye-stuffs at all. On formula (I) there is no particular reason why this should be so, but formula (II) provides a satisfactory explanation. Ortho and para quinones are known, but meta quinones do not exist, and hence the

absence of dyes in the meta series is to be expected on the quinonoid formula (II).

Structure (II), however, does not explain some important facts. It suggests that only one amino group is involved in the formation of the dye-stuff, and this is clearly erroneous. Crystal violet, with three *p*-dimethylamino groups, gives, as its name implies, brilliant violet solutions: if one of the amino groups is made into an ammonium ion, the colour changes to green, and closely resembles that of malachite green, in which there are two *p*-dimethylamino groups. This can be done in two ways: either excess of mineral acid can be added to the solution, when the ion (V) is formed, or the monomethiodide (VI) can be prepared. This fact indicates that the colour of crystal violet depends on the presence of the three —NMe₂ groups and that if one becomes quaternary, it is put out of action and the compounds (V) and (VI) have only two amino groups contributing to the colour. The argument can be carried a stage further. Addition of more acid to a crystal violet solution gives a weak orange colour which resembles that of the salt of a monodimethylamino-triphenyl carbinol; a further amino group has been made inactive. In the same way the diamino-triphenylmethane dyes of the malachite green group lose their intense colour if one of the two amino groups is converted into an ammonium kation either by addition of alkyl iodide or by excess of mineral acid. These facts have no immediate explanation on Nietzki's formula (II); neither will it account for the marked distinction between the strongly absorbing diamino and triamino compounds on the one hand and the more weakly absorbing mono-amino compounds on the other.

A further point of difficulty is that the formula offers no real explanation for the intense absorption of the salts. At the time when it was proposed, the fact that one of the rings was quinonoid was accepted as sufficient reason for this, but the discovery that quinone diimine and monoimine resemble quinone itself and are weakly coloured compounds (see p. 97) shows that such a view cannot be held. The same point is shown still more clearly by the properties of the Homolka bases. The only structure that can be allotted to these compounds is (IV), in which two of the rings are benzenoid and one quinonoid; but although in this respect they conform to the postulated conditions for a deeply coloured compound, the depth of their colour is no greater than that of a true quinone.

A course which has found a certain number of advocates is to abandon Nietzki's formula altogether and revert to that of Rosenstiehl (I), with the emendation that the chlorine atom is ionized, so that it is written as the salt (III) (p. 89) in which the carbon atom is carrying the positive charge.[1] The chief reasons for such a course were the discovery that true carbonium salts can exist and are coloured compounds. Triphenylmethyl perchlorate

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[1] See *inter alia* W. Dilthey, *J. pr. Chem.* 1925, **109**, 273; R. Wizinger, *Ber.* 1927, **60**, 1377; this view is held by a certain number of dye-chemists, e.g. H. E. Fierz-David, *Künstliche organische Farbstoffe*, Berlin, 1926, p. 209.

is formed by the interaction of triphenylmethyl chloride and silver per-chlorate in a mixture of benzene and nitrobenzene,[1] or by the action of perchloric acid on the carbinol in acetic anhydride; it forms red crystals and gives conducting solutions in tetrachlorethane,[2] and must be formu-lated as a salt, $[\phi_3 C^+]ClO_4$, in which the kation appears to contain a carbon atom with six valency electrons. These true carbonium salts are decom-posed by water into triphenylmethyl carbinol and the acid; the colour of their solutions varies widely with the solvent. The view that the tri-phenylmethane dye-stuffs are carbonium salts has little to recommend it.[3] It can only account for the marked difference in the absorption of the dyes and the true carbonium salts by allotting a vague auxochromic effect to the amino groups, and it can advance no simple reason for the enormous difference between the two sets of compounds in their stability towards water.

The arguments which support Nietzki's quinonoid formula are strong enough to show its essential correctness; its weaknesses can be removed by extending and emending it. In the formula of the ion of pararosaniline as written by Nietzki, one ring is quinonoid and the other two benzenoïd (VII).

VII.   VIII.

IX.
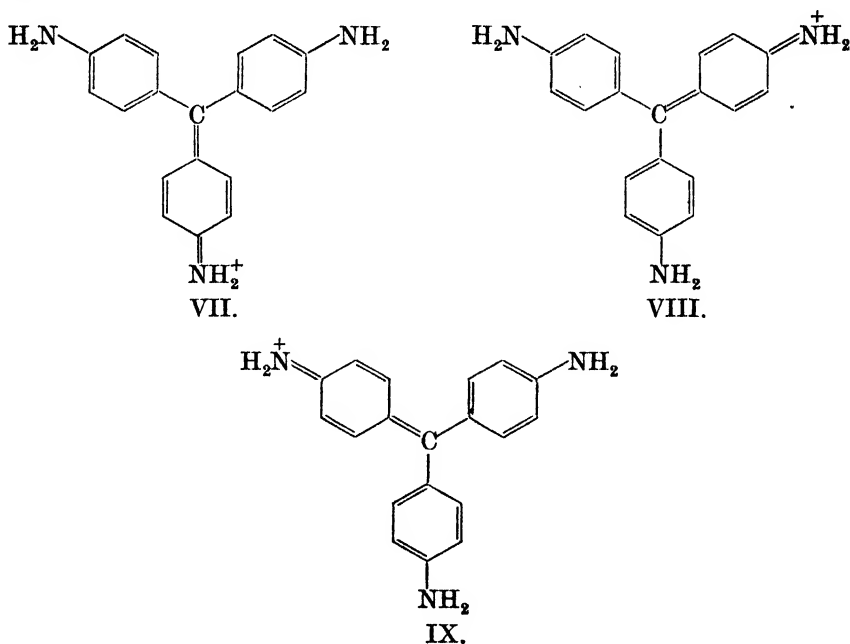
Such a structure differs from (VIII), in which a different ring is quinonoid, only in the distribution of electrons and not in the attachment of the con-stituent atoms. Yet a third formula (IX) can be written in which a

[1] M. Gomberg, and L. H. Cone, *Annalen*, 1909, **370**, 193.
[2] K. A. Hofmann, A. Metzler, and H. Lecher, *Ber.* 1910, **43**, 186.
[3] See F. Kehrmann, *Helv. Chim. Acta*, 1927, **10**, 670.

quinonoid structure is allotted to the remaining ring. When there are alternative formulae between which it is impossible to draw any distinction, resonance will come into play and the actual state of the ion will be that of a hybrid between those states in which all three amino groups and all three rings are identically equivalent. This view removes the difficulties which have been raised against Nietzki's original formula. If one amino group becomes a quaternary ammonium ion, it cannot be attached to a quinonoid ring and hence cannot contribute a possible state to the resonance-hybrid; the methiodide of crystal violet has thus the same colour as malachite green, and the methiodide of malachite green as the salts of mono-amino-triphenylcarbinol. Again, resonance demands two or more possible alternative states; hence the diamino and triamino compounds go together and are dye-stuffs, while the mono-amino compounds are quite different, because there is only one amino group. The absence of dye-stuff colour in the Homolka bases is also accounted for; the transference of the quinonoid structure from one ring to another would involve the migration of a hydrogen atom, and hence two formulae such as (X) and (XI) for an Homolka base cannot give a resonance-hybrid.
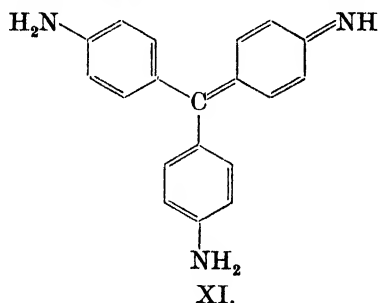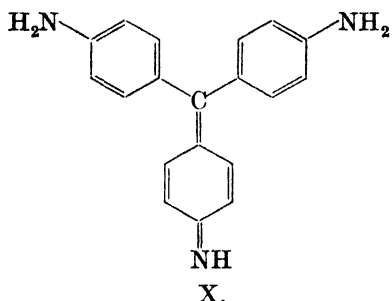
This view of the relation between the colour and the possibility of resonance which involves benzenoid and quinonoid structures finds further support in the fact that other classes of compounds, in which there is the possibility of a similar resonance, also show an intense absorption in the visible spectrum, and many of them are used as dyes.[1] Striking examples mentioned in this book are the cyanine dyes (p. 561) and the Wurster salts (p. 98); others occur in the natural pigments such as haemin and chlorophyll and in artificial pigments like the phthalocyanin lakes.

This conclusion, that the especial properties of pararosaniline arise from the fact that it is a resonating system in which all the amino groups and benzene rings participate, can be extended to all the dyes of the triphenylmethane group. In some of them, of course, all the resonating states are not identical. Methyl violet contains two dimethylamino groups and one monomethylamino group; when either of the former carry the positive charge, an identical state results, but when it is on the latter, the state is

[1] An interesting discussion of this point by C. R. Bury will be found in *J. Amer. C. S.* 1935, **57**, 2118.

different. The difference, however, is too small to cause a great disparity in the energy content of the states, so that it seems highly probable that all three states are of importance in the resonance. A great advantage of this view is that it gives a concrete meaning to the idea of an auxochromic group. This term has for long been used to indicate that the introduction of certain groups, called auxochromes, profoundly modifies the colour of a dye-stuff, but until the dyes were regarded as resonating systems, no precise reason for the effect could be advanced. Now it is clear that the principal reason is that the introduction of such a group means the creation of a new state which can participate in the resonating system.

There is one phenomenon shown by the triphenylmethane dyes which deserves attention. When a triamino dye is treated with acid, its colour changes first to that of a diamino dye and with further acid to the weak colour of a mono-amino compound; the reason for this, as has been explained, is that the amino groups are successively converted into ammonium ions. This salt formation, however, differs from the vast majority of similar reactions and is a slow process.[1] The observation is unexplained, but it seems not unlikely that an amino group which forms a state in a resonating system may differ from an ordinary amino group, and that a definite energy of activation may be needed to remove it from the resonating system.

There is the possibility that the true carbonium structure is also repre- sented in the resonating system of the ions of the dyes. It differs from the quinonoid structure only in electronic distribution. The point cannot be established until methods have been developed by which the nature of a resonating system can be thoroughly explored; but in so far as this possi- bility exists, it may be said that both of the conflicting views as to the constitution of the dyes contain an element of truth.

As has been mentioned above, the technical importance of the triphenyl- methane dyes has diminished since more stable compounds have been discovered which can replace them. The triphenylmethane dyes belong to the group of so-called basic dyes, the dye-stuff being a kation, and will combine directly with the protein of silk and less readily with that of wool. They cannot be used directly to dye cotton, presumably because they do not combine with cellulose; the cotton must first be treated with a mordant, for which purpose tannin is used, very often together with tartar emetic: metallic hydroxides, such as those of aluminium and iron, do not act as mordants for these dyes because there is no possibility of the formation of chelate co-ordination complexes. An enormous number of substituted triphenylmethane dyes have been prepared; introduction of substituents such as Cl, CH_3, SO_3H, and OAlk into the meta and any free para positions has only a small effect on the colour, though the sulphonic acid derivatives are naturally more soluble in water. In the ortho position, however, these substituents have the useful property of increasing the

[1] N. V. Sidgwick and T. S. Moore, *Z. phys. Chem.* 1907, **57**, 385; *J.C.S.* 1909, **95**, 889.

resistance of the colour to alkali. The decolorization by alkali is, as we have seen, due to the formation of the colourless carbinol-base. The effect of these substitu␞nts seems to be independent of the nature of the group and entirely determined by its position; hence it is probably a true steric effect, the ortho groups hindering the access of the hydroxyl ion to the central carbon atom and thus preventing the ready formation of the carbinol-base.

The dyes derived from the amino derivatives of diphenylmethane can be dismissed in a few words because their relationships and behaviour are very similar to those of the triphenylmethane series. An example of a carbinol-base of a diphenylmethane dye is Michler's hydrol,

$$Me_2N-\langle\ \rangle-CHOH-\langle\ \rangle-NMe_2,$$
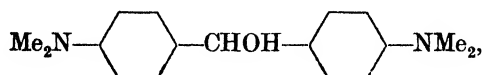
which has been mentioned already. This is converted by mineral acids into salts with a deep blue colour[1] which must contain the resonance-hybrid compounded from the possible states of the kation

$$Me_2^+N=\langle\ \rangle=CH-\langle\ \rangle-NMe_2.$$
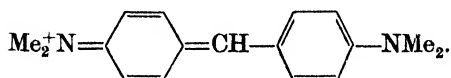
A technically more important substance is auramine, one of the purest yellow dyes known. It was originally obtained by heating together Michler's ketone and ammonium chloride in presence of zinc chloride, and the free base is the imine of the ketone.

$$\left(Me_2N\langle\ \rangle-\right)_2 C:O \xrightarrow{NH_4Cl} \left(Me_2N\langle\ \rangle-\right)_2 C:\overset{+}{N}H_2[Cl]$$
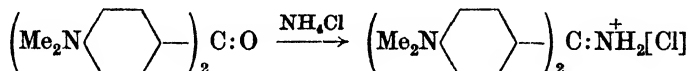
The usual method of preparation is to condense dimethylaniline with formaldehyde and heat the resulting tetramethyldiamino-diphenyl-methane with sulphur and ammonium chloride. The sulphur oxidizes the methylene group to a thio-ketone which reacts with the ammonium chloride.

$$2\,Me_2N\langle\ \rangle + CH_2O \longrightarrow \left(Me_2N\langle\ \rangle-\right)_2 CH_2$$

$$\longrightarrow \left(Me_2N\langle\ \rangle-\right)_2 CS \longrightarrow \left(Me_2N\langle\ \rangle-\right)_2 C:\overset{+}{N}H_2[Cl]$$
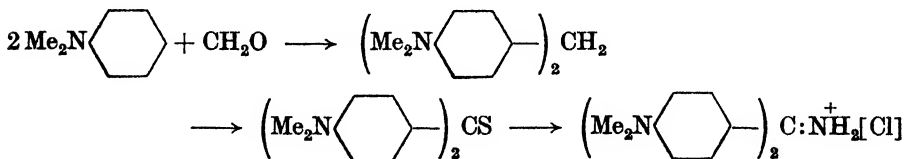
Which groups participate in the resonance in auramine is indicated by the fact that the acyl derivatives of auramine are not yellow dyes but are blue and resemble the dye-salts of diamino-diphenylmethane mentioned above.[2] The acyl group makes the imino nitrogen atom non-basic, so that

[1] W. Madelung and F. Völker, *J. pr. Chem.* 1927, **115**, 38.

[2] L. Semper, *Annalen*, 1911, **381**, 234.

the only possible states are those in which one of the dimethylamino groups carries the positive charge, i.e.

$$Me_2^+N{=}\langle\ \rangle{=}C{-}\langle\ \rangle{-}NMe_2 \quad [Cl].$$
$$\underset{NH\cdot CO\cdot\phi}{|}$$
(two states)
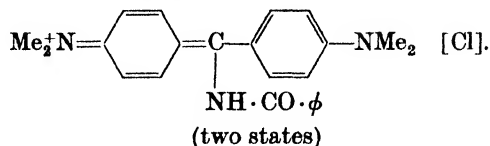
In auramine itself there is a further possibility and the colour of the dye is widely different:

$$Me_2\overset{+}{N}{=}\langle\ \rangle{=}C{-}\langle\ \rangle{-}NMe_2 \quad [Cl]$$
$$\underset{NH_2}{|}$$
(two states)

$$Me_2N{-}\langle\ \rangle{-}C{-}\langle\ \rangle{-}NMe_2 \quad [Cl].$$
$$\underset{NH_2^+}{||}$$
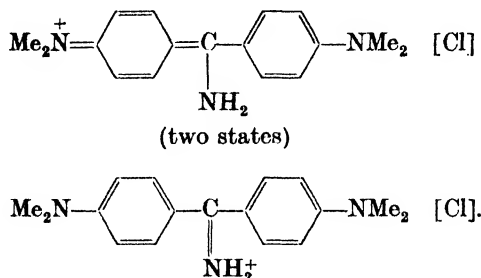
Silk can be dyed directly with auramine, but, as with the triphenylmethane dyes, cotton must be mordanted with tannin. The dye is unstable to boiling water, because it is hydrolysed to ammonia and Michler's ketone which is colourless because all possibility of resonating states is removed by the presence of the carbonyl group. The dye is valuable because of the purity of its colour and is used for colouring paper, cardboard, and leather.

Quinone Imines, Wurster Salts, and Related Compounds

Quinone diimine (I) and monoimine (II) are closely related to p-phenylenediamine and p-amino-phenol, respectively.

$$\text{I. } HN{=}\langle\ \rangle{=}NH \qquad \text{II. } HN{=}\langle\ \rangle{=}O$$
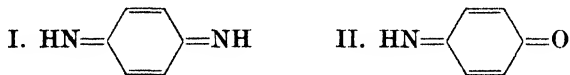
They may be regarded as derived from benzoquinone by replacing both or one of the oxygen atoms by imino groups. At the time when Nietzki's formula in its unmodified form was accepted for the triphenylmethane dye-stuffs, it was supposed that the compounds would show powerful absorption in the visible spectrum and many attempts were made to prepare them in order to confirm this prediction. Both compounds, however, are quite unstable, and it was only by working with special precautions that Willstätter[1] eventually obtained them. The diimine proved to be a colourless compound and the monoimine to have a pale sulphur-yellow colour.

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[1] R. Willstätter and E. Mayer, *Ber.* 1904, **37**, 1494; Willstätter and A. Pfannenstiehl, ibid. p. 4605.

The compounds can be obtained by two methods. When p-phenylene diamine and p-amino-phenol are oxidized with bleaching-powder, quinone dichlorimine (III) and the monochlorimine (IV) are formed. These are, respectively, colourless and yellow crystalline substances, volatile in steam and hydrolysed by dilute acids to quinone and ammonia. If these com-

III. ClN=⟨◯⟩=NCl   IV. ClN=⟨◯⟩=O
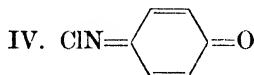
pounds are treated with hydrogen chloride in dry ether, chlorine is liberated, as in other cases of N-chlor compounds (see p. 41) and the imines are formed. The better method is to oxidize p-phenylenediamine or p-amino-phenol, by shaking their dry ethereal solutions with silver oxide or lead peroxide in presence of anhydrous sodium sulphate to remove the water produced. The isolation of the compounds is difficult and their preparation only succeeds if it is carried out in the dark and the materials are absolutely dry. Quinone diimine is a colourless crystalline substance which is explosive. It polymerizes very readily, especially by the action of light or acids, and in aqueous solution it darkens and decomposes: its molecular weight in boiling acetone corresponds to the simple formula. Quinone diimines with alkyl groups attached to the ring polymerize less readily and are more stable,[1] but all are very readily hydrolysed to ammonia and a quinone even by boiling water. Quinone monoimine resembles the diimine but is even more unstable: it decomposes in daylight in a few seconds.

By oxidation of N-substituted p-phenylenediamines under similar conditions Willstätter[2] obtained the methyl and dimethyl quinone diimines, $MeN:C_6H_4:NH$ and $MeN:C_6H_4:NMe$. These compounds are pale yellow unstable crystalline substances. The colour becomes more pronounced in the N-phenyl compounds: phenyl quinone diimine has been mentioned above as a product formed in the oxidation of aniline: the diphenyl compound, usually called quinone dianil, is more stable and can be obtained by bubbling oxygen through an alkaline solution in alcohol of N, N'-diphenyl-p-phenylenediamine.

The salts of all these diimines have practically the same colour as the free bases, but one of the most interesting facts known in this group of compounds is that there is a stage of oxidation half-way between the aromatic diamine and the quinone diimine, and that the salt belonging to this stage has an absorption spectrum quite different from that of either diamine or diimine. Comparatively sharp absorption bands appear and the appearance of the deeply coloured salt in solution recalls that of a triphenylmethane dye. In some cases these deeply coloured salts are stable in the solid state; two well-known examples are those obtained by oxidizing *asymm*-dimethyl-p-phenylenediamine and the tetramethyl compound

[1] F. Kehrmann and B. Cordone, *Ber.* 1923, 56, 2398; B. Cordone, *Helv. Chim. Acta*, 1924, 7, 956.   [2] *Ber.* 1905, 38, 2244.

with bromine. They are called, respectively, Wurster's red salt and blue salt after their discoverer.[1] These salts were at first thought to be those of the true diimine, such as $HN:C_6H_4:\overset{+}{N}Me_2$ [Br], but such a view could be easily disproved.[2] When p-amino-dimethylaniline is oxidized with bromine, the red colour reaches its maximum intensity if one atom of bromine is added for each molecule of diamine. With two atoms of bromine, the amount needed for oxidation to the quinone structure, the solution becomes colourless again. If the diamine is oxidized with nitrous fumes, the true quinone diimine nitrate $H_2\overset{+}{N}:C_6H_4:\overset{+}{N}Me_2$ $2[NO_3]_2$, can be isolated: it is a colourless compound, and with stannous chloride it is reduced first to Wurster's red salt and then to the colourless diamine. These facts are somewhat similar to those which have been observed in the oxidation of hydroquinone and the reduction of quinone: the former leads to quinone and the latter to hydroquinone, but in each case there is an intermediate stage, the formation of quinhydrone, an almost black insoluble compound.
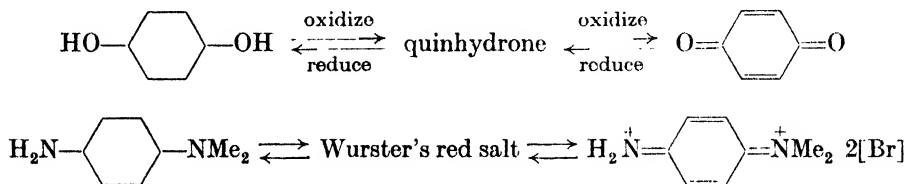
Since no simple formula is possible for an intermediate between the diamine and the diimine salt, Willstätter adopted a suggestion first made by F. Kehrmann,[3] that the Wurster salts are analogous to quinhydrones, i.e. that they are molecular compounds composed of one molecule of the diamine to one of the diimine salt, and he described the compounds as meriquinonoid, which means partially quinonoid.

This view obtained wide acceptance and the term meriquinonoid was extended to other classes of deeply coloured compounds. Thus the triphenylmethane dyes are often described as meriquinonoid compounds, because they were held to contain one quinonoid and two benzenoid nuclei. The term still has great significance in such cases, although it is no longer applicable in its original sense, for, as we have seen, it is incorrect to think of any difference between the three nuclei of a dye such as pararosaniline. On the other hand, the conception that Wurster's salts are molecular compounds composed of two molecules of mono-nuclear compounds raises the most serious difficulties, especially in the light of our knowledge of the true structure of quinhydrone. This latter compound, on analogy with which Kehrmann's view of the nature of Wurster's salts was largely based, is of high molecular weight and in the solid state consists

[1] C. Wurster et al. Ber. 1879, **12**, 1803, 1807, 2071; 1886, **19**, 3195, 3217.

[2] R. Willstätter and J. Piccard, ibid. 1908, **41**, 1462.

[3] Ibid. 1905, **38**, 3777.

of chains of alternate quinone and hydroquinone molecules joined together by co-ordinate links between oxygen and hydrogen,[1] e.g.:

$$...\text{—H}\leftarrow\text{O:}\text{:O}\rightarrow\text{H—O}\text{O—H}\leftarrow\text{O:}\text{:O}\rightarrow\text{H—O}\text{O—H}\leftarrow...$$
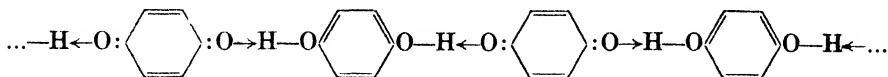
There is resonance with the form in which the quinonoid nuclei have become benzenoid and vice versa:

$$...\rightarrow\text{H—O}\text{O—H}\leftarrow\text{O:}\text{:O}\rightarrow\text{H—O}\text{O—H}\leftarrow\text{O:}\text{:O}\rightarrow\text{H—}...$$
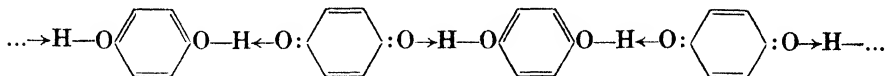
and there is no distinction between any two nuclei in the resonance-hybrid. Such a structure, however, can clearly never exist in dilute solution and it is an experimental fact that quinhydrone dissociates into its components in solution. The Wurster salts, however, retain their colour in solution, and with some of them large dilution of the solution makes no difference to the colour, as it would if they were complexes capable of dissociation.[2]

A further fact which cannot be reconciled with a meriquinonoid structure in its strict sense is that if the oxidation of a solution of the related diamines is followed by potentiometric titration, there are two distinct stages of oxidation, first to the Wurster salt and then to the diimine, and from the shape of the curve obtained it is possible to demonstrate that the first stage corresponds to an oxidation in which only one electron is removed from one molecule of the diamine.[3] If the Wurster salt is a true quinhydrone there is only one stage in oxidation, the diamine to the diimine, and this stage requires the removal of two electrons:

$$\text{Me}_2\text{N}\text{—}\langle\rangle\text{—NMe}_2 \longrightarrow \text{Me}_2^+\text{N}=\langle\rangle=\overset{+}{\text{N}}\text{Me}_2.$$
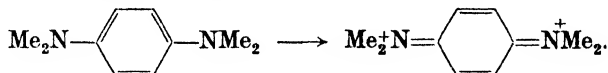
In view of these difficulties, the quinhydrone view must be abandoned, at least in solution, and a formula must be found for the Wurster salts in which there is only one nucleus. They are the salts of monacidic bases and their composition corresponds to a formula such as $[\text{Me}_2\text{N}\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2]\text{Br}$; the potentiometric results show that the kation of this salt is formed by loss of one electron from a molecule of the diamine.[4] Hence the kation must contain an odd number of electrons, and must be a free radical. This necessary conclusion that the Wurster salts are in essence free radicals was first put forward by A. Hantzsch,[5] and ably upheld by E. Weitz who had been working on analogous phenomena which occur among derivatives of $\gamma\gamma'$-dipyridyl.[6]

[1] O. R. Foz and J. Palacios, *Anal. soc. españ. fis. quim.* 1932, **30**, 421; *Zent.* 1932, ii, 3833.   [2] J. Piccard, *Annalen*, 1911, **381**, 357.

[3] L. Michaelis, *J. Amer. C. S.* 1931, **53**, 2953; Michaelis and E. S. Hill, ibid. 1933, **55**, 1481.

[4] L. Michaelis gives a comprehensive account of potentiometric measurements of this kind in *Chem. Rev.* 1935, **16**, 243.   [5] *Ber.* 1916, **49**, 511.

[6] E. Weitz and K. Fischer, ibid. 1926, **59**, 432; for a general account see E. Weitz, *Z. Elektrochem.* 1928, **34**, 538.

The Wurster salts in solution must, then, be regarded from the same point of view as other examples of free radicals, and their existence must depend on the same factors which determine the stability of compounds such as the aminium salts which have been discussed above (p. 64), and the nitrogen radicals of the type ϕ_2N (p. 388). In the two latter groups of compounds the free radical only exists when the nitrogen atom, which appears to show an abnormal valency, is directly linked to an aromatic nucleus, and the same is true for the Wurster salts; aliphatic diamines in which the amino groups are attached to a saturated carbon chain are not oxidized in any comparable manner. For this reason it is clear that the aromatic nucleus is intimately involved in the constitution of the free radical kation, and the whole of the behaviour of the compounds is best accounted for by the view that the kation is a resonance-hybrid of a number of structures, and its stability is due to the resonance. Two of the participating structures are clearly those in which one of the nitrogen atoms is unsaturated in that it has only seven electrons:

$$Me_2N—\bigcirc—\overset{+}{N}Me_2 \qquad Me_2\overset{+}{N}—\bigcirc—NMe_2 .$$
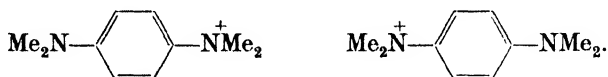
In addition to these structures there are others in which a carbon atom of the ring is unsaturated and the ring is ortho-quinonoid:

$$Me_2N—\bigcirc\overset{H}{=}\overset{+}{N}Me_2 .$$
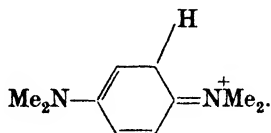
There will be four of these states because the molecule contains four similar CH groups.

The conclusion that the kation of a Wurster salt in solution is a resonance-hybrid of a number of structures, some of which contain a benzenoid and others a quinonoid ring, is of interest, not only because it gives some reason why the kation should exist at all, but also because it throws light on the resemblance between the colour of solutions of Wurster salts and of triphenylmethane dyes. The kation of a triphenylmethane dye such as pararosaniline is a resonance-hybrid of structures containing benzenoid and quinonoid rings in which three aromatic rings are involved. The Wurster salt contains a kation in which there is a very similar resonance, but only one nucleus. The fact that the dye-stuff colour is found, even though there is only one nucleus, indicates the true interpretation which should be put on the term meriquinonoid. Originally it meant a molecule or molecular complex which contained at least one benzenoid and one quinonoid ring, and if this is the definition, a compound like the kation of a Wurster salt cannot be meriquinonoid because there is only one nucleus. The resemblance between the kation of the triphenylmethane dye and that of the Wurster salt, shows that what the term meriquinonoid really

implies is not the co-existence of benzenoid and quinonoid structures in the same molecule, but resonance between those structures.

It is by no means certain that the conclusion we have reached as to the constitution of Wurster's salts in solution necessarily applies to all of these and similar compounds in the solid state.[1] Wurster's red salt forms green crystals as a solid, and the green colour is not due to a powerful reflection of green light as with fuchsine, but is the true colour of the crystal by transmitted light. This difference of colour is not found with Wurster's blue salt which gives blue crystals, and there is a marked difference in the stability of the two salts as solids: the blue crystals of the blue salt decompose rapidly, but the green crystals of the red salt can be kept for days without any change. These phenomena suggest that the solid red salt has a different constitution from the compound in solution, and it may well be that in the solid the free radicals mutually oxidize and reduce one another and form a mixture of the diamine and diimine which associate to give a true quinhydrone of high molecular weight. Piccard has found that the coloured salts derived from diamines show a colour in concentrated solution at a low temperature which is different from that of their true kations, particularly if the nitrogen atoms are not carrying many methyl groups, and this, too, is probably due to quinhydrone formation. The structure of the quinhydrone is, however, unknown.

Phenomena which resemble the formation of the Wurster salts also occur in the oxidation of other diamines. An example which has been mentioned already is the blue colour which is observed in the action of nitrous acid on diphenylamine in strong sulphuric acid (p. 62), and which is due to the oxidation of diphenyl benzidine, $\phi NH \cdot C_6H_4 \cdot C_6H_4 \cdot NH\phi$. In some of these cases there is a marked dependence of the depth of colour on dilution, and the actual nature of the coloured compound is doubtful.

Of the substituted quinone diimines and monoimines mention will be made of those in which one nitrogen atom is attached to an amino- or hydroxy-phenyl group. The three most interesting classes of these compounds are the following:

| Indamine | Indaniline | Indophenol |
| | (sometimes called Indophenol) | |
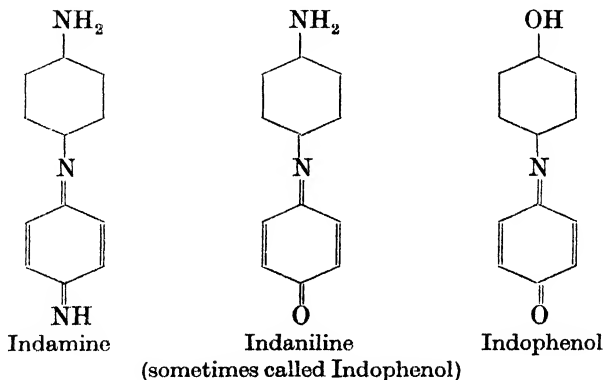
[1] J. Piccard, *Annalen*, 1911, **381**, 357; *Ber.* 1926, **59**, 1438.

The indamines are formed by oxidizing pp'-diamino-diphenylamines or a mixture of a p-phenylenediamine and an aniline. When an indamine forms a salt with one equivalent of acid, the resulting compound (V) has a structure very similar to that of a diamino-triphenylmethane dye-stuff (VI): there is the same possibility of resonance, the only difference being the nature of the atom uniting the nuclei. Consequently the indamine salts are dyes. The close parallel between the two groups is well shown in the absorption spectra; Bindschedler's green (VII), obtained by oxidizing a mixture of the hydrochlorides of N,N-dimethyl-p-phenylenediamine and dimethylaniline with bichromate, and malachite green (VI) not only show almost identical absorption as chlorides but give exactly the same colour changes when excess mineral acid is added and the colour fades, as has been described above.[1]
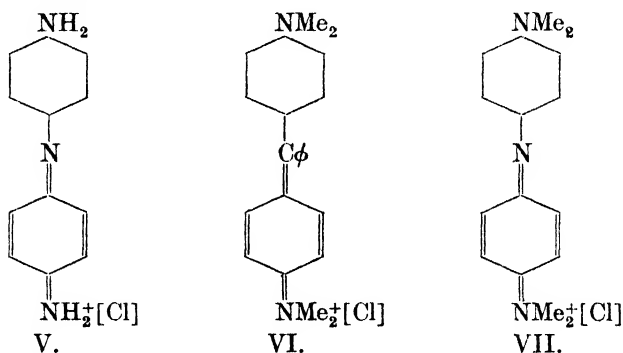
Somewhat similarly the derivatives of the other two classes behave as dye-stuffs, but these compounds are of little importance as such, because they are all quinone imines and are hydrolysed in acid solution to quinone and a diamine or amino-phenol; hence the dyes are not fast to acids. Naphthol blue (VIII), obtained by condensing p-nitroso-dimethylaniline with α-naphthol, is reduced to the colourless base (IX) which is soluble in alkali and can be applied to mordanted cotton; exposure to air oxidizes the leuco compound back to the dye on the fibre, so that the process resembles dyeing with indigo (see p. 507). This dye was formerly used as an indigo substitute, but because of its lack of fastness to dilute acids it was abandoned when indigo became cheap. Although these compounds are themselves of little use as dyes, they are closely related to valuable dyes of the phenazine and thiazine classes, and sometimes serve as intermediates for their preparation. In these dyes the two nuclei are further united by a nitrogen atom or by a sulphur atom, as in safranine (X), a desensitizer in photography, and methylene blue (XI).

Indophenol itself is an example of a compound in which the anion is a resonating system (XII): hence it dissolves in alkali to give a deep blue solution. This is the blue colour observed in Liebermann's reaction for nitroso compounds (see p. 453). Nitrosamines and other nitroso compounds

[1] F. Kehrmann, H. Goldstein, and A. v. Salis, *Helv. Chim. Acta*, 1927, **10**, 33.
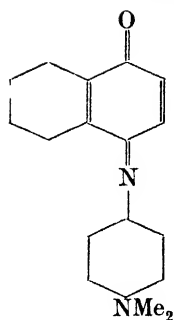
VIII.
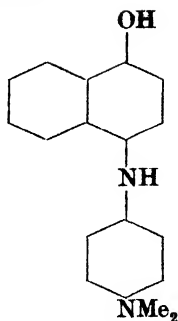
IX.
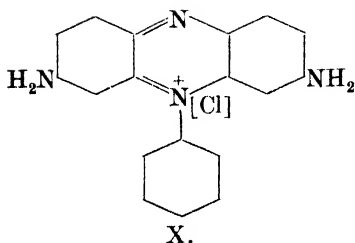
X.
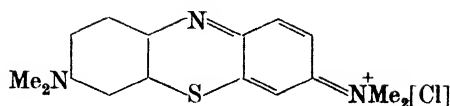
XI.
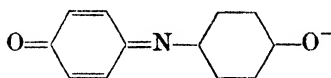
XII.

from which nitrous acid is eliminated by the action of strong sulphuric acid give the test because the nitrous acid reacts with the phenol to give *p*-nitrosophenol (p. 221), which condenses with more phenol to indophenol; when the product is poured into alkali, the blue colour of the anion (XII) appears.[1]

$$HO-\langle\ \rangle-NO + \langle\ \rangle-OH \longrightarrow O=\langle\ \rangle=N-\langle\ \rangle-OH.$$
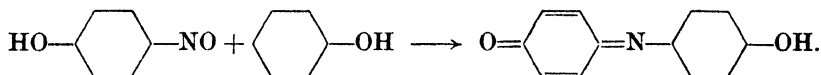
[1] H. Decker and B. Solonina, *Ber.* 1902, **35**, 3217.

AMINO-ACIDS

ALIPHATIC AMINO-ACIDS

THE compounds which contain both an amino group and a carboxyl group attached to a saturated carbon chain demand a separate and detailed discussion for two reasons. The first is that, because they are both basic and acidic, their properties differ widely from those of other substituted acids, and, indeed, from those of the majority of simple organic compounds; glycine, the simplest amino-acid, $CH_2(NH_2) \cdot CO_2H$, cannot be volatilized, is completely insoluble in organic solvents such as ether and benzene, and melts with decomposition at about 300°, while chloracetic acid, which has a larger molecular weight, boils at 189°, melts at 63°, and dissolves in organic solvents. The second reason is the close relationship that exists between the aliphatic amino-acids in which the amino and carboxyl groups are attached to the same carbon atom (α-amino-acids) and the peptides and proteins. The proteins are compounds of high molecular weight which form the chemical foundation of all living matter; the name covers a wide variety of substances which play many varied parts in living organisms; for example, the albumins and globulins act as food reserves as in the white of egg, in the haemoglobins and haemocyanins proteins are carriers of essential respiratory pigments, and the epidermal proteins constitute hair, wool, and silk, which act as protective materials. When proteins are hydrolysed by acids or bases they are converted very largely into a mixture of simple α-amino-acids. The relationship between proteins, peptides, and amino-acids is discussed later.

Since the methods of separation and purification of the aliphatic amino-acids are determined by their physical properties, it will be convenient first to give an account of their simple physico-chemical behaviour. The simple members of the class are colourless crystalline solids which are very soluble in water, hardly soluble in alcohol, and completely insoluble in all other solvents. They have no true melting-points, but decompose on heating at temperatures of 200–350°: the apparent melting-points vary widely according to the conditions of heating and are of little use for the identification of amino-acids. The apparent melting-point of glycine has been recorded by various workers at a series of temperatures from 210° to 292°.[1] These properties are very different from those of the aliphatic amines and of the carboxylic acids, and their occurrence does not depend on the relative position of the amino and carboxyl groups in the hydrocarbon chain; ε-amino-caproic acid, $H_2N \cdot (CH_2)_5 \cdot CO_2H$, in which the two groups are separated by five carbon atoms, behaves like glycine in

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[1] See M. S. Dunn and T. W. Brophy, *J. biol. Chem.* 1932, **99**, 221.

which there is only one. The properties resemble those of a true salt, such
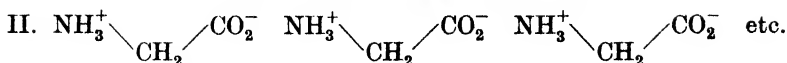as potassium chloride which melts at 613° and is insoluble in benzene.

The differences in physical properties between a crystalline salt and a
typical solid organic compound, such as benzoic acid, arise from the great
difference in the nature of the forces between the constituent units of the
two kinds of crystals. In potassium chloride the units from which the
crystal is built are the potassium and chloride ions, between which there
are powerful electrostatic forces; a crystal of benzoic acid is made up of
uncharged molecules, and there is no electrostatic attraction between
them, but only the much weaker van der Waals' forces. When a crystal
melts, the thermal energy of its units has become sufficient to overcome the
forces which hold them in the regular arrangement which constitutes the
crystal. The high melting-point of the salt and the much lower melting-
point of the organic compound are an indication of the different magnitude
of the forces involved in the two cases. The abnormally high solubility
of most salts in a solvent of high dielectric constant such as water and their
insolubility in hydrocarbon solvents is also a manifestation of the electro-
static forces between the ions in the crystal.

Now an amino-acid, $H_2N \cdot R \cdot CO_2H$,[1] contains both an acidic and a basic
group and salt formation can take place between them, just as it can
between ammonia and acetic acid. The properties of the crystalline amino-
acids afford a clear indication that the units in the crystal are held together
by ionic forces, and hence that the molecule must be written, not as
$H_2N \cdot R \cdot CO_2H$, but as an internal salt, $\overset{+}{H_3N} \cdot R \cdot CO_2^-$. Such a molecule is
neutral in so far as it has no total charge (it is conveniently referred to by
the German term zwitterion), but the forces between a collection of such
zwitterions are electrostatic, and of an entirely different nature from those
between the truly neutral molecules, $H_2N \cdot R \cdot CO_2H$. This view of the
constitution of the molecule of an aliphatic amino-acid in the solid state is
confirmed by more detailed investigation of crystalline structure.[2] The
crystals of the simple aliphatic amino-acids have a density (1·45–1·65)
which is greater than that of the majority of organic compounds, and this
shows that the packing is ionic. The arrangement of the molecules in the
crystal recalls that found in a true salt; each positive pole has as many
negative poles packed round it and vice versa as steric conditions will
permit. Glycine itself occurs in two different crystalline forms; one of
these is essentially built up of double molecules arranged positive charge
to negative charge (I), and the other of long chains of molecules arranged in
the same way (II):

$$
\text{I. } \overset{+}{H_3N} \diagup^{CH_2} \diagdown CO_2^- \\
\bar{O}_2C \diagdown_{CH_2} \diagup \overset{+}{N}H_3
$$

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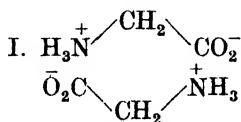
[1] R in what follows indicates a saturated chain of carbon atoms uniting the amino
and carboxyl groups.

[2] J. Hengstenberg and F. V. Lenel, *Z. Krist.* 1931, **77**, 424; J. D. Bernal, ibid.
78, 363.

II. $\underset{CH_2}{NH_3^+}\diagdown\diagup CO_2^-$ $\underset{CH_2}{NH_3^+}\diagdown\diagup CO_2^-$ $\underset{CH_2}{NH_3^+}\diagdown\diagup CO_2^-$ etc.

In aqueous solution an aliphatic amino-acid is an amphoteric electrolyte (ampholyte) and can form stable salts both with acids and with bases: in other words, it can exist both as the kation $H_3^+N \cdot R \cdot CO_2H$ and as the anion $H_2N \cdot R \cdot CO_2^-$. Since primary amines and carboxylic acids behave as weak electrolytes in aqueous solution, the dissociation of an amino-acid into its ions can be taken as governed by the law of mass-action and can be characterized by dissociation constants. If for purposes of simplification we restrict ourselves to very dilute solutions, activity coefficients can be neglected and the dissociation constants can be expressed as functions of the concentrations of the species involved in the dissociation equilibria. A simple acid which contains one amino and one carboxyl group, such as glycine, must have two dissociation constants, one governing its dissociation into the kation and the other into the anion, and these can be measured. Direct measurement of the conductivity of the acid itself cannot be used; the simple amino-acids only show a very small conductivity, and, since they are amphoteric electrolytes, this cannot be expected to follow Ostwald's dilution law and cannot be translated into dissociation constants.[1] There are two possible methods: the first is to measure the degree of hydrolysis of the two kinds of salts of the acid, say the hydrochloride and the sodium salt, and deduce from these the two dissociation constants, just as the dissociation constant of aniline as a base can be obtained from a knowledge of the degree of salt-hydrolysis of aniline hydrochloride. The second method is electrometric titration and consists essentially in observing the hydrogen-ion concentration, measured by means of a hydrogen electrode, which is brought about by addition of known amounts of strong acids and bases to the solution of the amino-acid.[2]

The dissociation constants so obtained are of value in throwing light on the constitution of the undissociated molecule of an amino-acid in aqueous solution. For this there are three possibilities: it may be entirely the uncharged molecule $H_2N \cdot R \cdot CO_2H$, or entirely the zwitterion,

$$H_3^+N \cdot R \cdot CO_2^-,$$
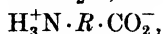
or both these forms may be present in appreciable quantity. For many years the first of these alternatives was accepted without any question and the two dissociation constants of an amino-acid were interpreted on this basis. The acid dissociation was taken as arising from the dissociation:

$$H_2N \cdot R \cdot CO_2H \rightleftharpoons H_2N \cdot R \cdot CO_2^- + H^+$$
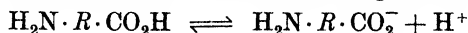
and the dissociation constant[3] as being $k_a = \dfrac{H^+ \times A^-}{A}$.

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[1] See C. W. Davies, *The Conductivity of Solutions*, London 1933, p. 193.

[2] See S. Glasstone, *The Electrochemistry of Solutions*, London, 1930, p. 343.

[3] In the following discussion concentration of the uncharged molecule $H_2N \cdot R \cdot CO_2H$ is written as A, that of the zwitterion $H_3^+N \cdot R \cdot CO_2^-$ as A^{+-}, that of the kation $H_3^+N \cdot R \cdot CO_2H$ as A^+, and that of the anion $H_2N \cdot R \cdot CO_2^-$ as A^-.

Similarly the basic dissociation constant was taken as $k_b = \dfrac{A^+ \times OH^-}{A}$ and as applying to the equilibrium:

$$H_2O + H_2N \cdot R \cdot CO_2H \rightleftharpoons OH^- + H_3^+N \cdot R \cdot CO_2H$$
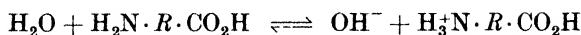
Values of the constants so calculated for four simple acids are shown in the second and third columns of the table: they are given as their negative logarithms, a system which has been widely adopted. Thus the acid dissociation constant of glycine is on this basis $10^{-9 \cdot 72}$ and is shown as $9 \cdot 72$.

	$-\log k_a$	$-\log k_b$	$-\log K_A$	$-\log K_B$
Glycine $CH_2(NH_2) \cdot CO_2H$	9·72	11·59	2·31	4·18
α-Alanine $MeCH(NH_2) \cdot CO_2H$ . . .	9·72	11·51	2·39	4·18
Leucine $Me_2CH \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$.	9·64	11·56	2·34	4·26
Taurine $CH_2(NH_2) \cdot CH_2 \cdot SO_3H$ . .	8·8	about 14	about − 0·1	5·1

It will be noticed that these results imply that the amino-acids are extremely weak as acids, much weaker than would be expected from their constitution. The first three compounds are carboxylic acids and the dissociation constants of carboxylic acids lie in the range 10^{-2} to 10^{-5}. The last, taurine, contains the sulphonic group, $—SO_3H$, which is a strong acid in the strict sense of the word and is completely dissociated in solution; on this basis, however, its dissociation constant is only $10^{-8 \cdot 8}$. The basic dissociation constants are equally unexpected; primary aliphatic amines have dissociation constants of the order of 10^{-4}, while as bases the amino-acids appear to be ten million times as weak.

The reason for these outstanding anomalies was pointed out first by E. Q. Adams,[1] and fully explained by N. Bjerrum in his classical paper on the constitution of the amino-acids.[2] He showed that the error lies in the initial assumption upon which the calculations are based. If instead of taking the undissociated species of the amino-acid to be the uncharged molecule $H_2N \cdot R \cdot CO_2H$, it is taken as the zwitterion $H_3^+N \cdot R \cdot CO_2^-$, the dissociation constants have values which lie close to those which would be expected.

Let us assume that the amino-acid in aqueous solution is the zwitterion. The dissociation in which the carboxyl group is involved must then be represented

$$H_3^+N \cdot R \cdot CO_2H \rightleftharpoons H_3^+N \cdot R \cdot CO_2^- + H^+$$
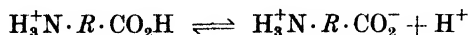
and the corresponding constant will be

$$K_A = \frac{A^{+-} \times H^+}{A^+}$$

[1] J. Amer. C. S. 1916, **38**, 1503.　　　　[2] Z. phys. Chem. 1923, **104**, 147.

The dissociation of the amino group will be

$$H_2O + H_2N \cdot R \cdot CO_2^- \;\rightleftharpoons\; HO^- + H_3^+N \cdot R \cdot CO_2^-$$
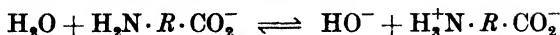
with a constant[1] $K_B = \dfrac{A^{+-} \times OH^-}{A^-}.$

The values of K_A and K_B can easily be obtained from those of k_a and k_b. The term A on the first assumption becomes A^{+-} on the second, and hence $K_A \times k_b = H^+ \times OH^- = K_W$, the ionic product of water which is a known quantity, and similarly $K_B \times k_a = K_W$. Inspection of the table shows that with this assumption of the zwitterion nature of the amino-acids the dissociation constants of their basic and acidic groups have reasonable values. Taurine, a sulphonic acid, has an acidic constant which cannot be measured accurately and is greater than one, while the three carboxylic acids fall together with constants of the order of 10^{-2}. This value is higher than that for the simple fatty acids (10^{-4} to 10^{-5}), a result which would be expected since in the dissociation of the carboxyl group the ease with which the positively charged proton leaves the molecule must be increased by the positive charge on the amino group. Similarly, the basic dissociation constants are of the same order of magnitude as those of other primary aliphatic amines. The older assumption led to a curious inversion; taurine which must be a strong acid appeared as an exceptionally weak base, and this fact alone is sufficient to prove its falsity.

The conclusion drawn from these considerations, that, as in the crystal, so in aqueous solution the aliphatic amino-acids exist almost entirely as zwitterions, is supported by other properties of their solutions. The most important of these is the dielectric constant. In the zwitterion of an α-amino-acid the positive and negative charges must be separated by a distance of at least $4\,A$, and thus the molecule must have an electric moment of the order of 18–$20\,D$ (4×10^{-8} cm. $\times 4 \cdot 771 \times 10^{-10}$ e.s.u.), a value much higher than that of the great majority of compounds. It is impossible to determine the electric moment directly, because the amino-acids are insoluble in non-polar solvents and are not volatile. An aqueous solution of an amino-acid, however, should have a dielectric constant greater than that of water itself because of the presence of molecules of such large moment. This prediction has been verified experimentally.[2] The amino-acids differ from the vast majority of organic compounds

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[1] Many writers formulate the dissociation of the amine group as follows:

$$H_3^+N \cdot R \cdot CO_2^- \;\rightleftharpoons\; H^+ + H_2N \cdot R \cdot CO_2^-.$$
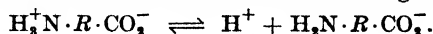
This leads to a dissociation constant, $K_B' = \dfrac{H^+ \times A^-}{A^{+-}}$ which is related to K_B above by the equation $K_B \times K_B' = K_W$ (the ionic product of water).

[2] R. Fürth, *Ann. Physik*, 1923, **70**, 63; O. Blüh, *Z. phys. Chem.* 1923, **106**, 341; G. Hedestrand, *Z. phys. Chem.* 1928, **135**, 36; G. Devoto, *Gazz.* 1930, **60**, 520; 1931, **61**, 897; *Z. Elektrochem.* 1934, **40**, 490; M. Frankenthal, *Z. phys. Chem.* 1932, B, **19**, 328; J. Wyman, Jr., and J. L. McMeekin, *J. Amer. C. S.* 1933, **55**, 908.

which are soluble in water in that when they are added to water the dielectric constant of the solution rapidly increases. This is direct evidence that the elect ic moments of the amino-acids in solution are much larger than that of water, and that the predominant form of the amino-acid is the zwitterion. In dilute solution the increase in dielectric constant is directly proportional to the concentration of the solute, as would be expected; at higher concentrations the increase is smaller, and finally there is no further increase. This effect probably arises from two causes. Firstly, at high concentrations there must be association of the dipoles of the amino-acids leading to double, or possibly more complicated, molecules of small moment, and secondly the viscosity of the solution increases, so that the molecules of solute can swing round less easily in the alternating electric field used in the measurements. The argument can be carried a stage farther. In a β-amino-acid the distance between the positive and negative charges must be greater than in an α-amino-acid, because there is one more carbon atom in the chain separating them. The electric moment should then be higher and the effect on the dielectric constant of water greater. Similarly a γ-amino-acid should have a yet greater effect. Again there is experimental verification: Wyman and McMeekin[1] obtained the following results in dilute solution for the increase in dielectric constant divided by the concentration of the solute (gm. mol. per litre).

	δ
Glycine, $H_3^+N \cdot CH_2 \cdot CO_2^-$	22·58
α-Alanine, $H_3^+N \cdot CHMe \cdot CO_2^-$	23·16
β-Alanine, $H_3^+N \cdot CH_2 \cdot CH_2 \cdot CO_2^-$	34·56
β-Amino-butyric acid, $H_3^+N \cdot CHMe \cdot CH_2 \cdot CO_2^-$	32·26
γ-Amino-valeric acid, $H_3^+N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CO_2^-$	54·8
ϵ-Amino-caproic acid, $H_3^+N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CO_2^-$ . . .	77·5

Attempts have been made to calculate from these results the actual values of the electric moments of the amino-acids and the shapes of their molecules. So many assumptions must, however be made that the values obtained do not have much significance.[2]

Other properties of aqueous solutions of amino-acids which afford evidence of the presence of zwitterions cannot be discussed here. It should, however, be pointed out that, although a zwitterion is not an ion in the sense that, carrying both a positive and a negative charge, it does not migrate in an electric field and hence does not contribute towards the conductivity of the solution, its presence does increase the number of electric charges in the solution (the ionic strength). This factor is of importance in many of the properties of a solution of an ordinary electrolyte, and is the reason for some of the great differences that exist between ionic and non-ionic solutions. Consequently solutions of amino-acids, although virtual non-conductors, resemble those of true salts in phenomena such as mutual solubility effects.[3]

[1] loc. cit.   [2] See W. Kuhn and H. Martin, *Ber.* 1934, 67, 1526.

[3] Further discussion of this aspect of the physical chemistry of solutions of

The deduction that must be made from the results described so far is that in aqueous solution an aliphatic amino-acid exists predominantly as a zwitterion, but the possibility is not excluded that a small fraction may be present as the uncharged molecule $H_2N \cdot R \cdot CO_2H$. There is consequently the further question as to the relative amount of zwitterion to uncharged molecule in solutions of the simple amino-acids. The question has been answered by the work of J. T. Edsall and M. H. Blanchard,[1] which is based on that of L. Ebert.[2] If we consider the acid dissociation constant of an amino-acid and assume that both zwitterion and uncharged molecule are present, the following equilibria must be set up:

$$H^+ + H_3^+N \cdot R \cdot CO_2^- \;\rightleftharpoons\; H_3^+N \cdot R \cdot CO_2H \;\rightleftharpoons\; H^+ + H_2N \cdot R \cdot CO_2H.$$
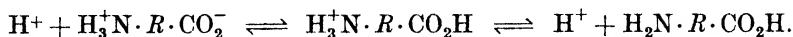
These will be characterized by two dissociation constants:

$$K_I = \frac{H^+ \times A^{+-}}{A^+}, \qquad K_{II} = \frac{H^+ \times A}{A^+}.$$

Hence the ratio of the concentrations of the two forms of the undissociated acid will be given by the following equation:

$$Z = \frac{A^{+-}}{A} = \frac{K_I}{K_{II}}.$$

The measured dissociation constant of the acid K_A must be determined by the equation:

$$K_A = \frac{H^+(A^{+-}+A)}{A^+} = K_I + K_{II}.$$

K_A can be determined experimentally, and if either K_I or K_{II} were known, the value of Z could be obtained from these two equations. Ebert pointed out that K_{II} can be taken as equal to the dissociation constant of the ester of the amino-acid. This involves the equilibrium

$$H_3^+N \cdot R \cdot CO_2Et \;\rightleftharpoons\; H^+ + H_2N \cdot R \cdot CO_2Et,$$
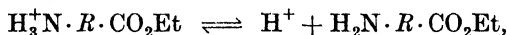
and this is identical with the equilibrium which is governed by K_{II} apart from the fact that —CO_2Et replaces —CO_2H, and it is known that these groups have the same effect on the ionic dissociation of another ionizable group in the molecule.[3] Hence if K_E is the dissociation constant of the ester, we can write $K_{II} = K_E$, a measurable quantity, and $K_I = K_A - K_E$. Z is then equal to $\dfrac{K_A - K_E}{K_E}$, or if K_A is much larger than K_E, which is true for the aliphatic amino-acids, $Z = K_A/K_E$. Some of the results of Edsall and Blanchard at 25° are given in the table, the dissociation con-

amino-acids will be found in: E. J. Cohn, *Naturwiss.* 1932, **20**, 663; *Science*, 1934, **79**, 83; G. Scatchard and J. G. Kirkwood, *Phys. Z.* 1932, **33**, 297; J. G. Kirkwood, *J. Chem. Phys.* 1934, **2**, 351.

[1] *J. Amer. C. S.* 1933, **55**, 2337.
[2] *Z. phys. Chem.* 1926, **121**, 385.
[3] R. Wegscheider, *Monatsh.* 1895, **16**, 153; 1902, **23**, 287.

stants again being expressed as their negative logarithms; the differences
between these is the logarithm of Z.

	$-\log K_A$	$-\log K_E$	$\log Z$	$\log Z$ alcohol
Glycine	2·31	7·73 (Et)	5·42	3·0
		7·66 (Me)		
α-Alanine	2·39	7·80	5·41	2·7
β-Alanine	3·60	9·13	5·53	3·1
ε-Amino-caproic acid . . .	4·43	10·37	5·94	2·8

The amount of zwitterion is thus 250,000 to 1,000,000 times greater than
that of the uncharged molecule for these simple amino-acids, so that for
the majority of purposes the presence of the latter can be neglected.

The effect of temperature on Z can be found by the same method.
K_A is known to be almost independent of temperature, but K_E increases
rapidly, so that as the temperature rises the relative amount of uncharged
molecule becomes greater; Z is approximately halved for each 10° rise.
According to the principle of Le Chatelier and Braun this must mean
that the process $H_2N \cdot R \cdot CO_2H \rightarrow H_3^+N \cdot R \cdot CO_2^-$ is exothermic, and the
temperature coefficient of Z shows that it is accompanied by the evolution
of $11\cdot5\pm1$ kilocals. The dissociation of the carboxyl group is known to
have practically no heat-effect, and thus the heat evolved comes from the
conversion of the amino group into a kation. The observed value agrees
well with the known heat of the reaction $RNH_2 + H^+ \rightarrow RNH_3^+$. The effect
of change of solvent can also be investigated, although here the assump-
tions which must be made decrease the numerical accuracy of the results.
The approximate values of $\log Z$ in 90 per cent. aqueous alcohol at 25°, are
shown in the table. In this solvent there is one uncharged molecule of
glycine to 1,000 zwitterions, instead of the 250,000 in water. From these
results it will be seen that both temperature and solvent have a profound
influence on the constitution of an amino-acid in solution.

Methods of Preparation

The majority of the methods described in Chapter II for the preparation
of aliphatic amines can be used for obtaining amino-acids, but in most of
them modifications must be introduced because of the special properties
of the products. The separation of an amino-acid from a reaction mixture
which contains inorganic salts is often a tedious process: the amino-acid
cannot be extracted with ether, and its solubility is very much the same
as that of the salts. With some amino-acids such as glycine the separation
can be effected by boiling the solution with freshly precipitated copper
oxide; the amino-acid forms a characteristic deep blue compound with
copper which can be crystallized from the solution and decomposed by
passing hydrogen sulphide into its aqueous solution. These compounds are
not true salts of copper; their solutions have only a very small conductivity[1]

[1] E. Abderhalden and E. Schnitzler, *Z. physiol. Chem.* 1927, **163**, 94.

and do not show the characteristic reactions of the cupric ion. They are co-ordination complexes of the structure:

$$
\begin{array}{ccc}
R \cdot CH\!-\!NH_2 & & O\!-\!CO \\
| & \diagdown Cu \diagup & | \\
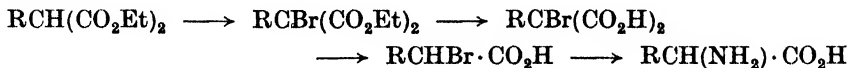CO\!-\!O & H_2N\!-\!CH \cdot R &
\end{array}
$$
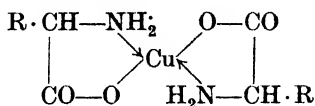
Another method for the separation of an amino-acid from inorganic salts is to add hydrochloric acid to the solution, and evaporate to dryness; the resulting solid is extracted with alcohol which dissolves the hydrochloride of the amino-acid and leaves most of the inorganic salts as residue. The aqueous solution of the hydrochloride is then treated with lead oxide or carbonate, and the insoluble lead chloride removed; addition of a little silver oxide removes the residual amount of chlorine. The solution is saturated with hydrogen sulphide, the lead sulphide filtered off and evaporation of the solution gives the amino-acid which can be recrystal-lized from water or aqueous alcohol.[1] The higher amino-acids and especially those, such as phenylalanine, $\phi \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$, which contain an aromatic residue, are sparingly soluble in cold water and their separation from a reaction mixture offers little difficulty.

The following are the more important methods of preparation.

(i) **From halogenated acids.** If an α-halogenated acid is treated at room temperature for some days with an excess of aqueous ammonia, a good yield of the amino-acid is obtained. Sometimes liquid ammonia in a sealed vessel is used. Although a large excess of ammonia is employed there is very little tendency to produce an imino-acid, $NH(R \cdot CO_2H)_2$; this is due to the basic group in the amino-acids being in the form $^+NH_3$—rather than NH_2— even in presence of much ammonia. Glycine is easily prepared from chloracetic acid by this method and is separated from the ammonium chloride either as its copper salt, or by addition of methyl alcohol.[2]

$$Cl \cdot CH_2 \cdot CO_2H + 2NH_3 \longrightarrow H_2N \cdot CH_2 \cdot CO_2H + NH_4Cl$$
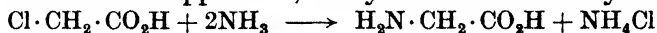
Emil Fischer's method[3] is very convenient for preparing α-amino-acids. The requisite alkyl group is introduced into malonic ester by the ordinary method, and the alkylmalonic ester brominated. Hydrolysis with concentrated hydrobromic acid at 50–60° gives the bromo-malonic acid, which loses carbon dioxide at 140–150°. The last stage is treatment with aqueous ammonia.

$$RCH(CO_2Et)_2 \longrightarrow RCBr(CO_2Et)_2 \longrightarrow RCBr(CO_2H)_2$$
$$\longrightarrow RCHBr \cdot CO_2H \longrightarrow RCH(NH_2) \cdot CO_2H$$

If an aliphatic amine is used in the place of ammonia, an N-alkyl amino-acid is formed; thus sarcosine (methylglycine), $MeNH \cdot CH_2 \cdot CO_2H$, is obtained by the action of aqueous methylamine on chloracetic acid.

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[1] For general methods of dealing with the soluble amino-acids see W. Cocker and A. Lapworth, *J.C.S.* 1931, 1391.

[2] *Organic Syntheses*, Collective vol. 1, p. 293.

[3] E. Fischer, *Ber.* 1904, **37**, 3062; Fischer and W. Schmitz, ibid. 1906, **39**, 351.

(ii) Gabriel's phthalimide reaction can be used in several ways. A halogen-substituted ester can be condensed with potassium phthalimide and the product hydrolysed to the amino-acid by heating with concentrated hydrochloric acid in a sealed tube at 200°.

$$\text{(phthalimide)}NK + Cl \cdot CH_2 \cdot CO_2Et \longrightarrow \text{(phthalimide)}N \cdot CH_2 \cdot CO_2Et$$

$$\longrightarrow H_2N \cdot CH_2 \cdot CO_2H$$

Another possibility is that used by Gabriel for the preparation of γ-amino-butyric acid. 1,3-Dibromopropane is treated with one equivalent of potassium cyanide, and the resulting γ-bromo-butyronitrile condensed with phthalimide. Hydrolysis of the product gives the desired acid.

$$Br \cdot (CH_2)_3 \cdot Br \longrightarrow Br \cdot (CH_2)_3 \cdot CN \longrightarrow \text{(phthalimide)}N \cdot (CH_2)_3 \cdot CN$$

$$\longrightarrow H_2N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CO_2H$$

A dibromo-paraffin can be condensed with one equivalent of phthalimide, and the product allowed to react with the sodium derivative of malonic ester: hydrolysis again gives the amino-acid.[1]

$$\text{(phthalimide)}N \cdot CH_2 \cdot CH_2Br \longrightarrow \text{(phthalimide)}N \cdot CH_2 \cdot CH_2 \cdot CH(CO_2Et)_2$$

$$\longrightarrow H_2N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CO_2H$$

Sörensen's extension[2] of the phthalimide method is important for the preparation of α-amino-acids. Phthalimido-malonic ester is easily obtained from potassium phthalimide and bromo-malonic ester.[3] It contains a hydrogen atom which can be replaced by an alkyl group by treatment with sodium and an alkyl halide. Heating with concentrated hydrochloric acid at a high temperature brings about hydrolysis, and at the same time carbon dioxide is lost to give the monocarboxylic amino-acid. Thus phenylalanine can be obtained from phthalimido-malonic ester and benzyl chloride.

$$\text{(phthalimide)}N \cdot CH(CO_2Et)_2 \longrightarrow \text{(phthalimide)}N \cdot C(CO_2Et)_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad | $$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_2\phi$$

$$\longrightarrow \quad H_2N \cdot CH \cdot CO_2H$$
$$\qquad\qquad\qquad\qquad | $$
$$\qquad\qquad\qquad\quad CH_2\phi$$

Modifications of this method can be used for substituted amino-acids. Hydroxy-amino-acids can be prepared by condensing a dibromo-paraffin

[1] W. Aschan, *Ber.* 1891, **24**, 2449.
[2] S. P. L. Sörensen, *Z. physiol. Chem.* 1905, **44**, 448.
[3] *Organic Syntheses*, Collective vol. 1, p. 266.

with one molecule of the sodium derivative of phthalimido-malonic ester, obtaining an acetyl derivative by the reaction of the remaining bromine atom with potassium acetate, and hydrolysing the product to the hydroxy-amino-acid. α-Amino-δ-hydroxy-valeric acid was prepared by Sörensen[1] by the following scheme:

This acid is of interest because on heating alone or with hydrochloric acid it is converted by loss of water into proline (pyrrolidine-α-carboxylic acid) which is found among the hydrolysis products of many proteins.

(iii) Reduction methods can be used, especially the reduction of a phenylhydrazone, oxime, or nitrile. Thus reduction of the phenyl-hydrazone of pyruvic acid gives alanine:

$$CH_3 \cdot CO \cdot CO_2H \longrightarrow \underset{N \cdot NH\phi}{CH_3 \cdot C \cdot CO_2H} \longrightarrow \underset{NH_2}{CH_3 \cdot CH \cdot CO_2H} + \phi NH_2.$$

An α-ketonic acid can also be converted into an amino-acid by reduction in presence of ammonia, either catalytically or with sodium amalgam or ferrous sulphate, or sometimes simply by another molecule of the ketonic acid. The change is a general one and can be represented by the equation:

$$R \cdot CO \cdot CO_2H + NH_3 + 2H \longrightarrow R \cdot CH(NH_2) \cdot CO_2H + H_2O.$$

It possibly proceeds through the unstable imino-acid which may be in equilibrium with the ketonic acid:

$$R \cdot CO \cdot CO_2H + NH_3 \rightleftharpoons \underset{NH}{R \cdot C \cdot CO_2H} + H_2O.$$

A special interest attaches to this reaction because it is an imitation of a reaction which occurs in the animal body. Ketonic acids, and especially pyruvic acid, are known to be break-down products of the sugars in metabolism, and G. Embden and E. Schmitz[2] have shown that when the ammonium salt of an α-ketonic acid is perfused through an isolated liver,

[1] S. P. L. Sörensen and A. C. Andersen, *Z. physiol. Chem.* 1908, **56**, 250.
[2] *Biochem. Z.* 1912, **38**, 393.

the corresponding α-amino-acid is formed; thus pyruvic acid yields alanine. This transformation is an essential link in the conversion of carbohydrates into amino-acids and thence into proteins which takes place in the animal body. The converse of this reaction also occurs, since it is known that in passing through the body α-amino-acids can be oxidized to ketonic acids which can be isolated from the urine,[1] and can also be transformed into carbohydrate and appear as glycogen in the liver.[2]

(iv) Addition of ammonia to an unsaturated acid (in the form of its ester) is not a reaction of great preparative importance, but presents certain points of interest. When an unsaturated ester, such as crotonic ester, is allowed to react with ammonia in solution in absolute alcohol, the principal reaction is addition of ammonia to the double bond with the formation of a β-amino-ester; interaction of the ammonia with the ester group to give an amide (see p. 137) hardly takes place.[3]

$$RCH:CH \cdot CO_2Et + NH_3 \longrightarrow RCH(NH_2) \cdot CH_2 \cdot CO_2Et$$
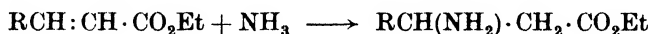
When a β-amino-acid is heated, the converse of this reaction occurs and the unsaturated acid is formed.

Reactions of this type also take place under the influence of enzymes; in the presence of bacteria an equilibrium is set up between fumaric acid and ammonia and l-aspartic acid, in which the latter predominates.[4]

$$\begin{array}{c} HO_2C \cdot CH \\ \| \\ HC \cdot CO_2H \end{array} + NH_3 \rightleftharpoons \begin{array}{c} CH_2 \cdot CO_2H \\ | \\ CH(NH_2) \cdot CO_2H \end{array}$$
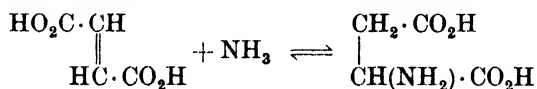
The most convenient synthesis of aspartic acid is to heat fumaric ester with alcoholic ammonia in a sealed vessel at 100°. The main product of the reaction is diketopiperazine diacetamide, the cyclic condensation product of two molecules of the mono-amide of aspartic acid, and this can be hydrolysed by alkali, when the free acid is obtained.[5]

$$\begin{array}{c} EtO_2C \cdot CH \\ \| \\ HC \cdot CO_2Et \end{array} + 2NH_3 \longrightarrow \begin{array}{c} CH_2 \cdot CONH_2 \\ | \\ CH(NH_2) \cdot CO_2H \end{array}$$

$$2 \begin{array}{c} CH_2 \cdot CONH_2 \\ | \\ CH(NH_2) \cdot CO_2H \end{array} \longrightarrow \begin{array}{c} CO \\ H_2NOC \cdot CH_2 \cdot CH \quad NH \\ NH \quad CH \cdot CH_2 \cdot CONH_2 \\ CO \end{array}$$

$$\longrightarrow 2 \begin{array}{c} CH_2 \cdot CO_2H \\ | \\ CH(NH_2) \cdot CO_2H \end{array}$$

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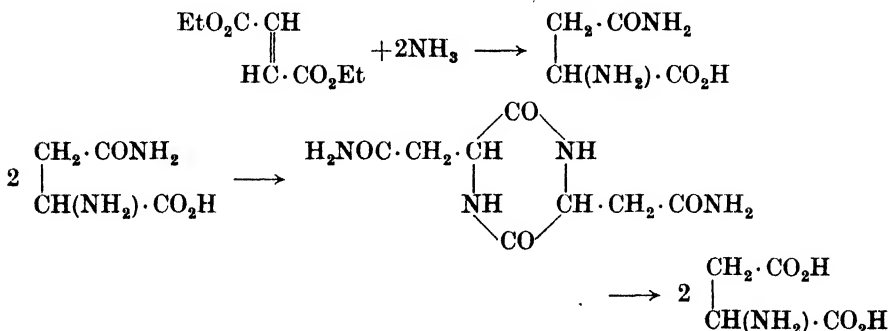
[1] O. Neubauer and co-workers, *Z. physiol. Chem.* 1910, **67**, 230; **70**, 1, 326; F. Knoop and E. Kertess, ibid. 1911, **71**, 252.

[2] J. S. Butts, M. S. Dunn, and L. F. Hallman, *J. biol. Chem.* 1936, **112**, 263.

[3] K. Morsch, *Sitz. Akad. Wiss. Wien*, 1932, **141**, 50, 677.

[4] J. H. Quastel and B. Woolf, *Biochem. J.* 1926, **20**, 545.

[5] M. S. Dunn and S. W. Fox, *J. biol. Chem.* 1933, **101**, 493.

† (v) A reaction which is often used for the preparation of α-amino-acids is that of Strecker,[1] who found that by the action of ammonia on the cyanhydrins derived from aldehydes or ketones or by that of prussic acid on the aldehyde-ammonias, the nitriles of α-amino-acids are formed and can be hydrolysed to the acids.

$$RR'C{:}O \xrightarrow{HCN} RR'C{\Big\langle}^{OH}_{CN} \xrightarrow{NH_3} RR'C{\Big\langle}^{NH_2}_{CN} \longrightarrow RR'C(NH_2){\cdot}CO_2H$$

$$RCH{:}O \xrightarrow{NH_3} RCH{\Big\langle}^{NH_2}_{OH} \xrightarrow{HCN} RCH{\Big\langle}^{NH_2}_{CN} {\text{-- --}}\to RCH(NH_2){\cdot}CO_2H$$
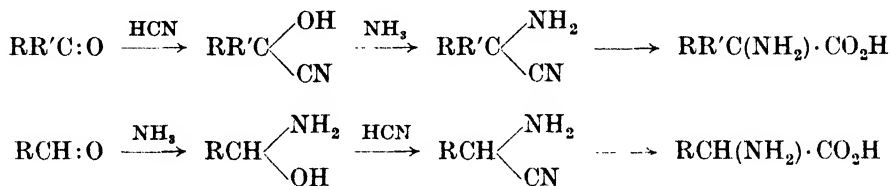
In practice the aldehyde or ketone is treated with a mixture of equivalent amounts of potassium cyanide and ammonium chloride and the amino-nitrile is hydrolysed without being separated. With soluble amino-acids it is better to use ammonia and prussic acid in order to avoid the separation from potassium chloride, and to hydrolyse by boiling with aqueous sulphuric acid which can be removed by addition of the equivalent of barium carbonate.[2] When formaldehyde is treated with ammonium chloride and potassium cyanide in presence of acetic acid, a crystalline condensation product of amino-acetonitrile, $H_2N{\cdot}CH_2{\cdot}CN$, and formaldehyde separates. The compound is usually called methylene-amino-acetonitrile and is given the formula $CH_2{:}N{\cdot}CH_2{\cdot}CN$, but its molecular weight is higher than that which corresponds with this formula.[3] This substance is a convenient source both of glycine and its ester. If it is heated with alcoholic hydrogen chloride, glycine ester hydrochloride, $[Cl]NH_3{\cdot}CH_2{\cdot}CO_2Et$, results; it can be hydrolysed to free glycine, best by treating it first with alcoholic sulphuric acid, when the formaldehyde residue is removed, and the acid sulphate of amino-acetonitrile crystallizes out, and then hydrolysing this with aqueous baryta.[4]

Strecker's reaction can be applied to substituted aldehydes. Thus Emil Fischer and H. Leuchs[5] converted glycollic aldehyde, $CH_2OH{\cdot}CHO$, into β-hydroxy-α-amino-propionic acid, $CH_2OH{\cdot}CH(NH_2){\cdot}CO_2H$, the racemic form of serine which is a product of the hydrolysis of silk.

(vi) α-Amino-acids containing aromatic residues can be prepared by the so-called azlactone method of Erlenmeyer.[6] When hippuric acid, the benzoyl derivative of glycine and a readily obtainable compound, is heated with an aromatic aldehyde and sodium acetate in acetic anhydride, an oxazolone (often called an azlactone) is formed. This is hydrolysed to an

[1] *Annalen*, 1850, **75**, 27.

[2] W. Cocker and A. Lapworth, *J.C.S.* 1931, 1391.

[3] W. Klages, *Ber.* 1903, **36**, 1508; T. B. Johnson and M. W. Rinehart, *J. Amer. C. S.* 1924, **46**, 770.

[4] W. K. Anslow and H. King, *J.C.S.* 1929, 2463; *Organic Syntheses*, Collective vol. 1, 292, 347.

[5] *Ber.* 1902, **35**, 3787.　　　　　　　　[6] *Annalen*, 1904, **337**, 205.

N-benzoyl unsaturated acid, which can be reduced to the saturated acid and the benzoyl group removed by hydrolysis.

$$\begin{array}{c} \text{ArCHO} + \underset{\substack{|\\ \text{NH}\cdot\text{CO}\cdot\phi}}{\text{CH}_2\cdot\text{CO}_2\text{H}} \longrightarrow \underset{\substack{|\\ \text{N}:\text{C}\cdot\phi}}{\text{ArCH}:\text{C}\!\!-\!\!\text{CO}}\!\!>\!\!\text{O} \longrightarrow \underset{\substack{|\\ \text{NH}\cdot\text{CO}\cdot\phi}}{\text{ArCH}:\text{C}\cdot\text{CO}_2\text{H}} \\[2mm] \longrightarrow \underset{\substack{|\\ \text{NH}\cdot\text{CO}\cdot\phi}}{\text{ArCH}_2\cdot\text{CH}\cdot\text{CO}_2\text{H}} \longrightarrow \underset{\substack{|\\ \text{NH}_2}}{\text{ArCH}_2\cdot\text{CH}\cdot\text{CO}_2\text{H}} \end{array}$$
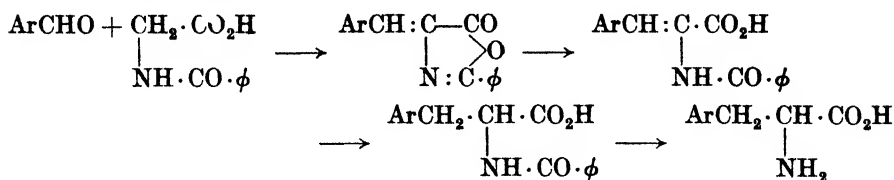
The reduction and hydrolysis can be performed all in one stage from the azlactone by heating with hydriodic acid and red phosphorus; if excess of hydriodic acid is used, the product is the amino-acid, but with smaller amounts the N-benzoyl acid can be obtained, and this is often useful for purposes of optical resolution (see below).[1] Tyrosine, which is p-hydroxyphenylalanine, $HO\!-\!\bigcirc\!-\!CH_2\cdot CH(NH_2)\cdot CO_2H$, has been synthesized by this method and also the iodine-containing amino-acid, thyroxine (I) which is the active principle of the thyroid gland.[2]

I. $HO\!-\!\bigcirc\!-\!O\!-\!\bigcirc\!-\!CH_2\cdot CH(NH_2)\cdot CO_2H$

(with I substituents on the rings)
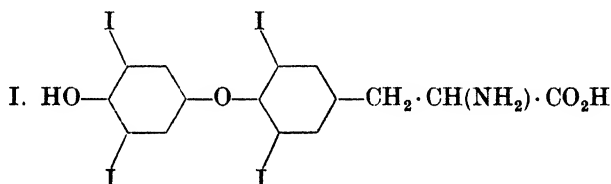
(vii) β-Amino-acids are often most conveniently prepared by the Hofmann degradation of the imide of a succinic acid. Succinimide itself gives β-alanine.[3]

$$\underset{\substack{|\\ \text{CH}_2\!\!-\!\!\text{CO}}}{\text{CH}_2\!\!-\!\!\text{CO}}\!\!>\!\!\text{NH} \longrightarrow \underset{\substack{|\\ \text{CH}_2\cdot\text{CONH}_2}}{\text{CH}_2\cdot\text{CO}_2\text{H}} \longrightarrow \underset{\substack{|\\ \text{CH}_2\cdot\text{NH}_2}}{\text{CH}_2\cdot\text{CO}_2\text{H}}$$
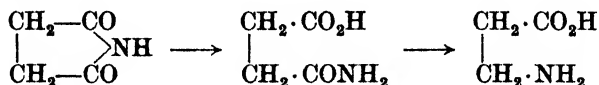
Optical Resolution of Amino-acids

All the amino-acids obtained as hydrolysis products of proteins are α-amino compounds, and hence, with the exception of glycine, they contain at least one asymmetric carbon atom, $R\cdot CH(NH_2)\cdot CO_2H$. The acids so obtained are optically active, unless the conditions of hydrolysis have been so vigorous that racemization has taken place. Amino-acids prepared by synthetical methods are, of course, optically inactive, and for comparison with the acids from natural sources they must be resolved. The simple acids with one amino and one carboxyl group are too feebly acidic to form stable salts with the optically active alkaloids, and hence the usual method of resolution is to prepare an acyl derivative,

$$R\cdot CO\cdot NH\cdot CHR'\cdot CO_2H,$$
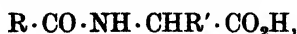
[1] J. Lamb and W. Robson, *Biochem. J.* 1931, **25**, 1231.
[2] C. R. Harington and G. Barger, *Biochem. J.* 1927, **21**, 169.
[3] F. H. Holm, *Arch. Pharm.* 1904, **242**, 590.

resolve this by means of an optically active base (brucine, strychnine, and cinchonine are often used), and remove the acyl group by hydrolysis. As acyl group the benzoyl group has been used, but it is often better to use the formyl derivative, $H \cdot CO \cdot NH \cdot CHR' \cdot CO_2R$, which is easily prepared by boiling the amino-acid with anhydrous formic acid. These derivatives are more readily hydrolysed than the benzoyl compounds, and thus there is less risk that during the hydrolysis the optically active amino-acid will be racemized.

There are marked physiological differences between the two enantio-. morphous forms of an active amino-acid. The dextro form of alanine which occurs in nature has a much sweeter taste than the laevo-enantiomorph, and similar phenomena are found with most α-amino-acids.[1] The magnitude and sign of the rotation of the optically active α-amino-acids is an interesting and complicated subject which cannot be discussed here. There is, however, evidence that in all the enantiomorphs which are obtained from proteins the arrangement of the four groups attached to the α-carbon atom is identical.[2] This statement does not mean that they all show the same sign of rotation, since whether a compound shows dextro- or laevo-rotation depends both on the solvent and the temperature, and mode of combination. Alanine from natural sources is dextro-rotatory while its ethyl ester is laevo-rotatory; natural valine, $Me_2CH \cdot CH(NH_2) \cdot CO_2H$, is dextro-rotatory both in water and dilute hydrochloric acid, but natural leucine, $Me_2CH \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$ is laevo-rotatory in aqueous solution and dextro-rotatory in hydrochloric acid.

Chemical Properties of the Amino-acids

The aliphatic amino-acids can be converted into their ethyl esters by heating with absolute alcohol and hydrogen chloride. The solution after standing or evaporation deposits the crystalline hydrochloride of the ester.

$$H_2N \cdot CH_2 \cdot CO_2H \longrightarrow [Cl]H_3N \cdot CH_2 \cdot CO_2Et$$
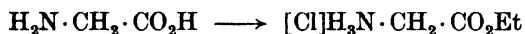
The esters are distinctly less stable than those of unsubstituted carboxylic acids, and to obtain the free ester from its hydrochloride the latter must be treated with caustic soda at a low temperature, and the mixture immediately extracted with ether. The ethyl and methyl esters of the lower amino-acids are basic oils, miscible with water, alcohol, and ether. Replacement of the hydrogen atom of the carboxyl group by an alkyl radical makes zwitterion formation impossible, and the esters do not resemble salts in their physical properties. They can be distilled under reduced pressure without decomposition, a fact of the greatest importance for the separation of amino-acids (see p. 125). They are hydrolysed more readily than the majority of esters. The esters of α-amino-acids when

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[1] See H. Brockmann, 'Das biologische Verhalten stereoisomerer Verbindungen', *Stereochemie*, ed. Freudenberg, Leipzig, 1933, p. 921.

[2] E. Fischer and K. Raske, *Ber.* 1908, **41**, 893; G. W. Clough, *J.C.S.* 1918, **113**, 526; P. Karrer and W. Kaase, *Helv. chim. Acta*, 1919, **2**, 436; 1920, **3**, 244.

heated under atmospheric pressure are converted into the so-called anhydrides of the amino-acids by loss of alcohol. The same change also takes place if the ester is kept for some time at room temperature. These anhydrides are diketo-piperazines.

$$RHC{\overset{\displaystyle CO_2Et}{\underset{\displaystyle NH_2}{\bigg<}}} \quad + \quad {\overset{\displaystyle H_2N}{\underset{\displaystyle EtO_2C}{\bigg>}}}CHR \quad \longrightarrow \quad RHC{\overset{\displaystyle CO-NH}{\underset{\displaystyle NH-CO}{\bigg<}}}{\bigg>}CHR$$
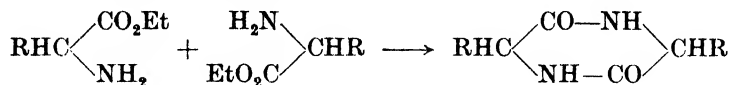
Diketo-piperazine (glycine anhydride) is also formed when glycine itself is heated in a sealed tube to 160°, together with a polymeric anhydride of the same composition, but of much greater molecular weight. This is a long-chain compound belonging to the class of the polypeptides:

$$-NH \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO-$$

The other α-amino-acids behave in a similar way on heating. β-Amino-acids lose ammonia when heated and give αβ-unsaturated acids; thus β-alanine gives acrylic acid at 200°.

$$H_2N \cdot CH_2 \cdot CH_2 \cdot CO_2H \quad \longrightarrow \quad NH_3 + CH_2{:}CH \cdot CO_2H$$
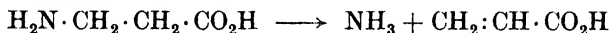
The γ- and δ-amino-acids lose water when heated and are converted into cyclic amides, often called lactams. At their melting-points γ-amino-butyric acid gives α-pyrrolidone, and δ-amino-valeric acid α-piperidone; these lactams are hydrolysed back to the amino-acids when they are heated with mineral acids.

$$H_2N \cdot (CH_2)_3 \cdot CO_2H \quad \longrightarrow$$

$$\begin{array}{c} CH_2-CH_2 \\ | \qquad | \\ CH_2 \quad CO \\ \diagdown \ \diagup \\ NH \end{array}$$

α-Pyrrolidone

$$H_2N \cdot (CH_2)_4 \cdot CO_2H \quad \longrightarrow$$

$$\begin{array}{c} CH_2 \\ \diagup \ \diagdown \\ CH_2 \quad CH_2 \\ | \qquad | \\ CH_2 \quad CO \\ \diagdown \ \diagup \\ NH \end{array}$$

α-Piperidone
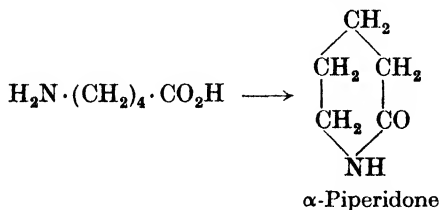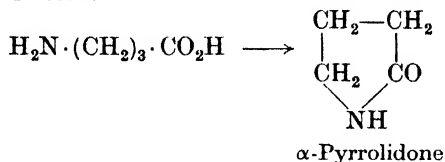
The way in which the length of the carbon chain separating the amino and carboxyl groups determines the nature of the product formed on heating recalls the very similar behaviour of the hydroxy-acids. Cyclic esters (lactones), just like lactams, are only formed with ease when they contain a five- or six-membered ring; in both cases this is due to the fact that the probability of the close approach of the two ends of the chain of atoms is greatest when the chain contains five or six members.

The N-acyl derivatives of the amino-acids, such as benzoylglycine (hippuric acid), $\phi \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H$, are useful not only for purposes of optical resolution, but also for their separation and identification. They are crystalline compounds which are sparingly soluble in cold water and

behave as true carboxylic acids. They can be prepared by shaking a solution of the amino-acid in aqueous caustic soda or sodium carbonate or bicarbonate with an acid chloride. The acyl derivative which is formed remains in solution in the alkali and is precipitated on acidification. Emil Fischer found that the β-naphthalene-sulphonyl derivatives were especially valuable because of their small solubility in water;[1] the sodium salt of β-naphthalene sulphonic acid is, however, sparingly soluble both in water and dilute hydrochloric acid, and care must be taken to avoid confusion of this salt with the sulphonyl derivative of the amino-acid.[2] 3,5-Dinitrobenzoyl chloride is also a very useful reagent,[3] which reacts almost instantaneously with simple amino-acids in presence of caustic soda; it is less reactive towards amino-acids which contain two carboxyl groups, such as aspartic acid, $HO_2C \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$, and can be used to separate aspartic acid from the monocarboxylic amino-acids.

The amino-acids show several other reactions which are typical of aliphatic amines. They condense readily with cyanic acid in aqueous solution to give carbaminyl derivatives (ureido-acids), a reaction similar to the formation of urea from ammonia and cyanic acid (see p. 276). Glycine gives hydantoic acid which is sparingly soluble in water, and is converted by heating with hydrochloric acid into its lactam, hydantoin.

$$HNCO + H_2N \cdot CH_2 \cdot CO_2H \longrightarrow H_2N \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H \longrightarrow$$

Hydantoin
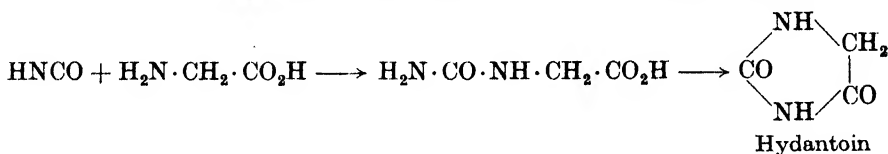
The amino-acids behave as primary aliphatic amines towards nitrous acid in aqueous solution and are rapidly converted into hydroxy-acids.[4]

$$RCH(NH_2) \cdot CO_2H + HNO_2 \longrightarrow RCH(OH) \cdot CO_2H + N_2 + H_2O$$
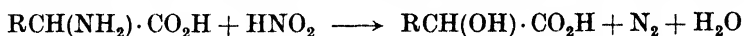
This reaction is the basis of van Slyke's method[5] for determining the percentage of free amino groups in amino-acids, peptides, and proteins. The gases evolved in the reaction consist of nitrogen, formed as shown in the equation above, and nitric oxide from the spontaneous decomposition of nitrous acid.

$$3HNO_2 \longrightarrow HNO_3 + 2NO + H_2O$$

Before the estimation the air in the apparatus is displaced by nitric oxide. The evolved gases are collected over alkaline permanganate solution which absorbs the nitric oxide, and the volume of residual nitrogen is measured. Certain amino-acids do not give the volume which would be expected from the above equation because of secondary reactions which take place, so that empirically determined correction factors must be used.[6]

[1] *Ber.* 1902, **35**, 3779.   [2] E. Fischer, ibid. 1906, **39**, 4144.

[3] B. C. Saunders, *Biochem. J.* 1934, **28**, 580.

[4] For the mechanism of this reaction see T. W. J. Taylor, *J.C.S.* 1928, 1897.

[5] *J. biol. Chem.* 1911, **10**, 15; 1912, **12**, 275.

[6] For details of the method see C. A. Morrow and W. M. Sandstrom, *Biochemical*

Amino-acids can also be estimated by volumetric titration. In aqueous solution they show a neutral reaction and do not give any apparent end-point when titrated with either acids or alkalis. With alteration of the solvent, however, volumetric estimation becomes possible. There are three principal volumetric methods.[1] The first was devised by Sörensen,[2] and is usually called formol-titration; it consists in adding to the aqueous solution of the amino-acid excess of a carefully neutralized solution of formaldehyde, and titrating with a standard strong alkali with phenol-phthalein or thymolphthalein as indicator. Caustic soda can be used in the absence of carbonates, but baryta is better. The monoamino-mono-carboxylic acids behave towards the alkali as mono-basic acids, and by matching the end-point against a control solution good results are obtained. There has been much discussion as to whether the method estimates carboxyl groups or amino groups. The original explanation of the method was that the acid $H_2N \cdot R \cdot CO_2H$ was too weak to be titrated by alkalis, but that the formaldehyde condensed with the amino group to give a methylene-amino-acid, $CH_2:N \cdot R \cdot CO_2H$, which was a stronger acid because the basic properties of the amino group had been removed. There is little doubt that this explanation is erroneous and that the method really estimates amine groups and not carboxyl groups.[3] The amino-acid is present in solution as the zwitterion $H_3^+N \cdot R \cdot CO_2^-$ which is incapable of reacting with formaldehyde; when alkali is added the amino-acid is converted into $H_2N \cdot R \cdot CO_2^-$, and this contains a free amino group, which condenses with the formaldehyde to give a stable anion. Thus the primary neutralization reaction is

$$OH^- + H_3^+N \cdot R \cdot CO_2^- \longrightarrow H_2O + H_2N \cdot R \cdot CO_2^-$$
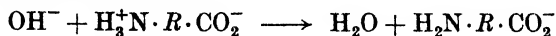
and the carboxyl group is not involved.

The other two methods depend on a different principle; the amino-acid is dissolved in a solvent of dielectric constant quite different from that of water. The result of this is that the values of its dissociation constants are different from those in water and with the right choice of indicator the titration can be carried out. The method of F. W. Foreman[4] and of R. Willstätter and E. Waldschmidt-Leitz,[5] consists in titrating with alkali in presence of a large amount of alcohol with phenolphthalein as indicator. With the simple amino-acids the alcohol must be at least 97 per cent. by volume, and thus alcoholic potash is used as alkali. The neutralization process is the same as that shown above, and the method estimates amino groups. The other method is that of K. Linderström-Lang:[6] the amino-

Laboratory Methods, New York, 1935, p. 123; *Handbuch der Pflanzenanalyse*, ed. G. Klein, Vienna 1933, vol. iii, p. 104; on the accuracy of the method, see R. A. Gortner and W. M. Sandstrom, *J. Amer. C. S.* 1925, **47**, 1663.

[1] A good paper on the volumetric estimation of amino-acids is by D. D. van Slyke and E. Kirk, *J. biol. Chem.* 1933, **102**, 651.　　　　[2] *Zent.* 1908, i, 143.

[3] M. Levy, *J. biol. Chem.* 1933, **99**, 767; G. M. Richardson, *Proc. Roy. Soc.* 1934 B, **115**, 121.　　　　[4] *Biochem. J.* 1920, **14**, 451.

[5] *Ber.* 1921, **54**, 2988.　　　　[6] *Z. physiol. Chem.* 1928, **173**, 32.

acid in aqueous acetone (95 per cent. of the latter) is titrated with alcoholic hydrogen chloride with naphthyl red (benzene-azo-α-naphthylamine) as indicator. The disadvantage of this method is the insolubility of amino-acids in acetone, but this can be overcome by adding the acetone in portions as the titration proceeds. The neutralization process is

$$H^+ + {}^-O_2C \cdot R \cdot NH_3^+ \longrightarrow HO_2C \cdot R \cdot NH_3^+$$
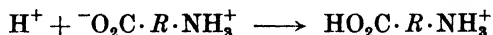
and the method estimates carboxyl groups.

Betaines

When glycine is treated with methyl iodide in methyl alcoholic solution the chief product is a solid which resembles glycine itself in its physical properties, but contains three methyl groups attached to nitrogen, as is shown by the fact that on boiling with caustic alkalis trimethylamine is evolved. This compound is called betaine and must be allotted the structure $Me_3^+N \cdot CH_2 \cdot CO_2^-$; it is an internal salt and can be regarded as the dehydration product of the quaternary ammonium hydroxide,

$$[OH]Me_3N \cdot CH_2 \cdot CO_2H.$$
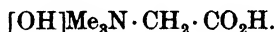
It is extremely soluble in water to give a neutral solution and insoluble in ether; it melts with decomposition at about 300°. Its structure was formerly written as though it contained a heterocyclic ring.

$$\begin{array}{c} CH_2\!\!-\!\!CO \\ | \qquad | \\ Me_3N\!\!-\!\!\!-\!\!O \end{array}$$
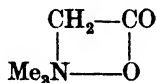
This formula is clearly erroneous, firstly because it implies that nitrogen can form five covalencies (see p. 32), and secondly because it takes no account of the salt-like nature of the compound. Betaine occurs widely in nature, especially in plant juices; it is present in quantity in residues left from the preparation of beet-sugar. It can be obtained in various ways; methylation of glycine or of sarcosine (methyl-glycine, $CH_2(NHMe) \cdot CO_2H$) with methyl iodide gives the quaternary iodide of the methyl ester, [I] $Me_3N \cdot CH_2 \cdot CO_2Me$, which is converted into betaine by silver oxide:

$$[HO]Me_3N \cdot CH_2 \cdot CO_2Me \longrightarrow MeOH + Me_3^+N \cdot CH_2 \cdot CO_2^-.$$
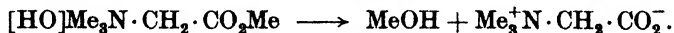
It is also formed when an aqueous solution of chloracetic acid and trimethylamine is heated:

$$Me_3N + Cl \cdot CH_2 \cdot CO_2H \longrightarrow Me_3^+N \cdot CH_2 \cdot CO_2^-$$
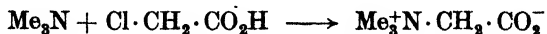
Betaine behaves as a base and forms stable crystalline salts by addition of a molecule of a monobasic acid; its hydrochloride has the structure $[Cl]Me_3N \cdot CH_2 \cdot CO_2H$.

Betaine is isomeric with the methyl ester of dimethylamino-acetic acid, $Me_2N \cdot CH_2 \cdot CO_2Me$. This compound can be obtained from dimethylamine and methylchloracetate, and is quite different from betaine in its

properties; it is a liquid which boils without decomposition at 135°, and is miscible with water and organic solvents. When heated to 170–200° in a sealed tube it is converted into betaine by migration of a methyl group:

$$Me_2N \cdot CH_2 \cdot CO_2Me \longrightarrow Me_3^+N \cdot CH_2 \cdot CO_2^-.$$

The change is to some extent reversible, since betaine is partially converted into the isomeric methyl ester when heated above 300°.

The tendency to form compounds analogous in structure to betaine is common to the esters of all acids which contain a tertiary amino group, but the ease with which the betaine is formed varies within wide limits. In general ethyl esters form betaines less readily than methyl esters; the ethyl ester of diethylamino-acetic acid, $Et_2N \cdot CH_2 \cdot CO_2Et$, is not converted into triethyl-betaine, $Et_3^+N \cdot CH_2 \cdot CO_2^-$, on heating, and this latter compound is best obtained by the action of ethyl iodide on the ester, to give $[I]Et_3N \cdot CH_2 \cdot CO_2Et$, followed by the action of silver oxide. Betaines can be obtained from all amino-acids, not only the α-amino compounds, and their physical properties are always salt-like, irrespective of the length of the carbon chain which separates the amino and carboxyl groups. The betaines of β- and γ-amino-acids undergo changes on heating which are similar to those which take place in the Hofmann degradation by exhaustive methylation (see p. 28). Thus trimethyl-propiobetaine gives trimethylamine and acrylic acid.

$$Me_3^+N \cdot CH_2 \cdot CH_2 \cdot CO_2^- \longrightarrow Me_3N + CH_2 : CH \cdot CO_2H$$
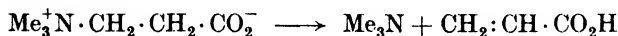
The Separation of Amino-acids

It has been mentioned already that hydrolysis of proteins by acids, alkalis, or enzymes gives a mixture which mainly consists of certain α-amino-acids. The first step towards elucidating protein structure is the separation and identification of these acids. This is by no means a simple task, both because of the complexity of the mixture and because of the physical properties of the amino-acids. The following is a list of the more important acids which have been isolated from proteins, but it is not complete.

Monoamino monocarboxylic acids:

Glycine (glycocoll),	$CH_2(NH_2) \cdot CO_2H$
Alanine	$CH_3 \cdot CH(NH_2) \cdot CO_2H$
Valine	$Me_2CH \cdot CH(NH_2) \cdot CO_2H$
Norleucine	$CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$
Leucine	$Me_2CH \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$
Isoleucine	$MeEtCH \cdot CH(NH_2) \cdot CO_2H$
Serine	$CH_2(OH) \cdot CH(NH_2) \cdot CO_2H$

Sulphur-containing acids:

Cysteine	$CH_2(SH) \cdot CH(NH_2) \cdot CO_2H$
Cystine	$HO_2C \cdot CH(NH_2) \cdot CH_2 \cdot S \cdot S \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$
Methionine	$Me \cdot S \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$

Diamino-monocarboxylic acids:

Ornithine	$CH_2(NH_2) \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$
Lysine	$CH_2(NH_2) \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$
Arginine	$H_2N \cdot C(:NH) \cdot NH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$
Citrulline	$H_2N \cdot CO \cdot NH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$

Monoamino-dicarboxylic acids:

Aspartic acid	$HO_2C \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$
Glutamic acid	$HO_2C \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$
β-Hydroxy-glutamic acid	$HO_2C \cdot CH_2 \cdot CH(OH) \cdot CH(NH_2) \cdot CO_2H$

Aromatic amino-acids:

Phenylalanine $\phi \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$

Tyrosine $HO—\langle\ \rangle—CH_2 \cdot CH(NH_2) \cdot CO_2H$

Heterocyclic acids:

Histidine

Tryptophane

Proline

Hydroxy-proline

Proteins, when hydrolysed, give mixtures of from ten to twenty amino-acids. Some of these can be separated without difficulty; thus the hydrochloride of glutamic acid is sparingly soluble in hydrochloric acid, so that if the protein is hydrolysed with that acid, most of the glutamic acid separates on cooling and standing. Arginine and histidine can be precipitated as silver salts from solution in baryta.

The first general method for separating all the acids was that of Emil Fischer.[1] It consists in converting the mixture of acids into the hydrochlorides of their ethyl esters with absolute alcohol and hydrogen chloride, liberating the free esters, best by sodium ethoxide[2] or barium oxide,[3] and distilling them under reduced pressure (0·1–12 mm.). A partial separation

[1] *Z. physiol. Chem.* 1901, **33**, 151.   [2] E. Abderhalden, ibid. 1922, **120**, 207.
[3] P. A. Levene, *J. biol. Chem.* 1909, **6**, 419.

is achieved in the fractional distillation, and the acids obtained by the hydrolysis of the esters are purified by recrystallization. The non-volatile residue contains tyrosine, arginine, histidine, and lysine. It is impossible to give here the details of what is a lengthy and toilsome operation; it has, however, been used successfully for the analysis of the amino-acid content of many proteins. An improvement can be effected by using Dakin's butyl alcohol separation[1] as a first stage. The aqueous solution of the mixed amino-acids is extracted continuously with warm butyl alcohol. Proline and hydroxy-proline are readily soluble in butyl alcohol, the mono-amino-monocarboxylic acids are soluble in the warm moist alcohol and crystallize out when the water is distilled off and the solution cooled, and all the other acids are insoluble. The monoamino-monocarboxylic acids can then be separated by Fischer's method; the basic acids can be precipitated from the aqueous residue with phosphotungstic acid, and the dicarboxylic acids can be separated by means of certain of their salts. It should be realized that owing to the difficulties in these methods the amino-acids actually isolated seldom make up more than about 75 per cent. of the total which must have been present, and that a protein should yield more than its own weight of amino-acids since the hydrolysis involves the addition of water at each of the peptide (—NH—CO—) linkages.

Peptides and the Relation of the Amino-acids to the Proteins

There is no doubt as to the nature of the chief link which unites the constituent amino-acids of a protein. It is easily broken by hydrolysis, and this fact suggests at once that it is similar to that in an amide and that the units are joined, amino group to carboxyl group, by elimination of water;

$$R \cdot NH_2 + HO_2C \cdot R' \longrightarrow R \cdot NH \cdot CO \cdot R'.$$
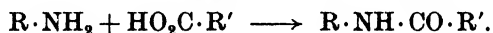
A further possibility is that ester linkages may be involved, but the proportion of the naturally occurring acids which contain alcoholic hydroxyl groups is too small to make this linkage of primary importance. This conclusion is supported by the fact that, although a protein contains relatively few free amino and carboxyl groups, the number of these groups, estimated by the methods described above, rapidly increases as the hydrolysis of a protein proceeds.

For this reason the compounds which are built up of two or more molecules of amino-acids linked together by amide formation are of especial interest. Their preparation is the first step towards the synthesis of the proteins, and the study of how their properties change with increase of molecular weight throws light on the complicated phenomena of protein behaviour. The compounds are called peptides and are classified according to the number of amino-acid residues which they contain. Thus two molecules of glycine can give rise to the dipeptide glycyl-glycine,

$$H_2N \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H.$$
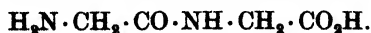
[1] H. D. Dakin, *Biochem. J.* 1918, 12, 290; *J. biol. Chem.* 1920, 44, 499.

Like all peptides it contains a free amino group and a free carboxyl group, and can be transformed into the tripeptide,

$$H_2N \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H,$$

and so on. Those of high molecular weight are described as polypeptides.

The first peptide to be synthesized was glycyl-glycine which Emil Fischer and E. Fourneau[1] obtained by hydrolysing diketopiperazine with acids:

$$\longrightarrow H_2N \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H.$$
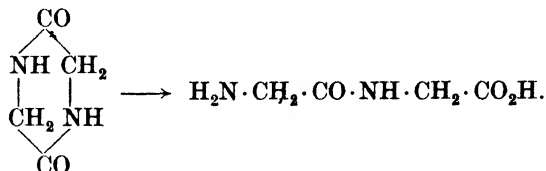
Such a method is obviously restricted to the formation of dipeptides only, and cannot be applied to the synthesis of compounds containing a number of amino-acid residues arranged in a desired order. The general scheme of such a method would be to take an amino-acid $H_2N \cdot R \cdot CO_2H$, prepare from it a compound $HRN \cdot R \cdot CO_2H$, where R is a substituent which will protect the amino-group, transform the carboxyl group into a derivative which will react with another amino-group, carry out the condensation with another amino-acid, and obtain the peptide derivative

$$HRN \cdot R \cdot CO \cdot NH \cdot R' \cdot CO_2H.$$
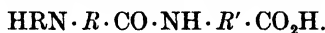
Removal of the protecting group R would give the peptide itself. Fischer devised a method of this kind. He used the carbethoxy group as the group R, and introduced it by the action of chloroformic ester:

$$EtO_2C \cdot Cl + H_2N \cdot R \cdot CO_2H \longrightarrow EtO_2C \cdot NH \cdot R \cdot CO_2H.$$
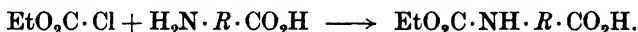
He then converted the carboxyl group into the acid chloride so that it reacted readily with the amino group of the ester of another amino-acid. By this means, starting with glycyl-glycine, he obtained carbethoxy-glycylglycyl-leucine ester, $EtO_2C \cdot (NH \cdot CH_2 \cdot CO)_2 \cdot NH \cdot CH(C_4H_9) \cdot CO_2Et$. He found it impossible, however, to remove the protecting group from the terminal amino group by hydrolysis without breaking the whole peptide chain into its amino-acid constituents. At about the same time Curtius[2] devised another scheme. He started with hippuric acid in which the benzoyl group protects the amino-group of glycine: from this he prepared the acid azide which reacts with an amino-acid in alkaline solution to form a peptide link:

$$\phi CO \cdot NH \cdot CH_2 \cdot CO \cdot N_3 + H_2N \cdot CH_2 \cdot CO_2H$$
$$\longrightarrow \phi CO \cdot NH \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H + HN_3.$$
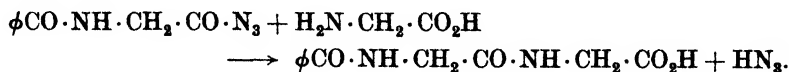
By repetition of the process he obtained benzoyl-pentaglycylglycine, but he could not remove the benzoyl group without destroying the compound.

Fischer then abandoned this line of attack and devised his classical

[1] Ber. 1901, 34, 2868.   [2] J. pr. Chem. 1904, 70, 57.

synthesis of the polypeptides. The essence of this method is to introduce the terminal amino group last of all. A simple example is as follows: glycylglycine is treated with chloracetyl chloride and the resulting acid on standing for some days with concentrated aqueous ammonia gives the tripeptide:

$$ClCH_2 \cdot COCl + H_2N \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H$$
$$\longrightarrow ClCH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H$$
$$\longrightarrow H_2N \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H.$$
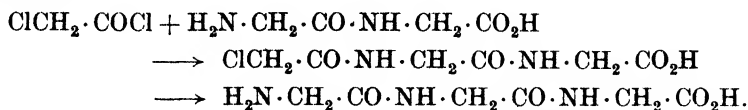
Many modifications of this method were devised; the first step goes better if the halogen-acid halide is condensed with the ester of an amino acid and not with the free acid; the product of the first step, a carboxylic acid, can be converted into its acid chloride by phosphorus pentachloride in acetyl chloride solution and condensation repeated with another molecule of an amino-acid or its ester before the final introduction of the free amino group, and in this way a peptide with many amino-acid residues can be prepared. It was also found possible to obtain the hydrochloride of the acid chloride of certain of the simpler amino-acids and to condense these directly with another amino-acid or peptide.

$$[Cl]NH_3 \cdot CH_2 \cdot COCl + H_2N \cdot R \cdot CO_2H \longrightarrow [Cl]NH_3 \cdot CH_2 \cdot CO \cdot NH \cdot R \cdot CO_2H$$
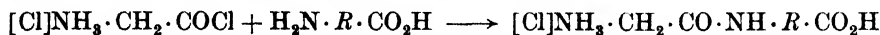
These acid chlorides are difficult to prepare; phosphorus pentachloride in acetyl chloride is used, but special apparatus is necessary to protect them from atmospheric moisture during filtration and washing. By these methods many peptides have been prepared, principally those containing the simpler monoamino-monocarboxylic acids. Those with the longest chain which have been synthesized are an octadeca-peptide with eighteen amino-acid residues, l-leucyl-triglycyl-l-leucyl-triglycyl-l-leucyl-octaglycyl-glycine which Fischer made in 1907,[1] and a nonadeca-peptide prepared by E. Abderhalden and A. Fodor in 1916.[2] The molecular weight of the former is 1,213 and of the latter 1,326.

The classical method of peptide synthesis breaks down when the attempt is made to introduce some of the more complicated amino-acids which are known to occur in the proteins. Hydroxy-amino and diamino acids react in a complicated fashion with phosphorus pentachloride and the desired halogen compounds cannot be obtained. The aromatic acids also offer difficulties. Thus glycyl-phenylalanine,

$$H_2N \cdot CH_2 \cdot CO \cdot NH \cdot \underset{\underset{CH_2\phi}{|}}{CH} \cdot CO_2H,$$

can be prepared, but not phenylalanylglycine,

$$H_2N \cdot \underset{\underset{CH_2\phi}{|}}{CH} \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H,$$

because in the last stage of the synthesis of the latter the action of

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[1] *Ber.* 1907, **40**, 1754. [2] Ibid. 1916, **49**, 561.

ammonia does not introduce an amino group, but splits out hydrogen bromide to give a cinnamic acid:

$$\begin{array}{c} Br \\ \diagdown \\ \phi CH_2 \diagup \end{array} CH \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H \longrightarrow \phi CH{:}CH \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H.$$

Some of these difficulties have been overcome by special methods. The aromatic acids can be introduced by the ingenious azlactone method of M. Bergmann.[1] An example of this is the preparation of d-tyrosyl-d-arginine. The acetyl derivative of p-hydroxybenzaldehyde is converted into the azlactone (see p. 117) by heating with acetylglycine; this reacts with the α-amino group of d-arginine in acetone solution to give a diacetyl unsaturated peptide, which can be reduced catalytically; the acetyl groups can be hydrolysed with hydrochloric acid without destroying the peptide.

$$MeCO \cdot O{-}\langle\rangle{-}CHO \longrightarrow MeCO \cdot O \cdot C_6H_4 \cdot CH{:}\underset{\underset{N=C \cdot Me}{|}}{C}{-}\underset{}{C}O\,{\diagup}\!O$$

$$\longrightarrow MeCO \cdot O \cdot C_6H_4 \cdot CH{:}C \cdot CO \cdot NH \cdot \underset{\underset{CO_2H}{|}}{CH} \cdot (CH_2)_3 \cdot NH$$
$$\qquad\qquad\qquad \underset{NH \cdot COMe}{|}\qquad\qquad\qquad\qquad \underset{C({:}NH)NH_2}{|}$$

$$\longrightarrow HO \cdot C_6H_4 \cdot CH_2 \cdot \underset{\underset{NH_2}{|}}{CH} \cdot CO \cdot NH \cdot \underset{\underset{CO_2H}{|}}{CH} \cdot (CH_2)_3 \cdot \underset{\underset{C({:}NH)NH_2}{|}}{NH}$$

A general method of peptide synthesis which will make it possible to link together amino-acids of any type in any desired order must be in essence the original scheme outlined above. In that scheme it is necessary to protect an amino group which is to be free in the final product, and the method broke down because the protecting groups used by Fischer and Curtius could not be removed without hydrolysing the whole peptide chain. Many attempts have been made to overcome this difficulty by using other protecting groups, and two methods have been found which are of importance. The first[2] is to convert the ester of an amino-acid into its p-toluene sulphonyl derivative, and prepare from this the acid hydrazide; then, as in Curtius's method, the azide obtained from the hydrazide is coupled with an amino-acid in alkaline solution. The crucial stage, the removal of the protecting sulphonyl group, can be achieved by warming with strong hydriodic acid to 50–60°, when the sulphonamide group is not hydrolysed, but reduced to form the thiophenol and the free amine:

$$H_2N \cdot R \cdot CO_2H \longrightarrow ArSO_2 \cdot NH \cdot R \cdot CO \cdot N_3$$
$$\longrightarrow ArSO_2 \cdot NH \cdot R \cdot CO \cdot NH \cdot R' \cdot CO_2H$$
$$\longrightarrow ArSH + H_2N \cdot R \cdot CO \cdot NH \cdot R' \cdot CO_2H.$$

The second is the so-called carbo-benzoxy method of M. Bergmann and

[1] M. Bergmann and co-workers, *Annalen*, 1926, **449**, 277; *Z. physiol. Chem.* 1927, **167**, 91; 1928, **175**, 154; 1930, **187**, 183; *Ber.* 1929, **62**, 1905.

[2] E. Fischer, ibid. 1915, **48**, 93; R. Schönheimer, *Z. physiol. Chem.* 1926, **154**, 203.

L. Servas;[1] this is of wide application and is one of the most important contributions to peptide chemistry. When benzyl alcohol is treated with a toluene sol..tion of phosgene, the benzyl ester of the half acid chloride of carbonic acid, $\phi CH_2 \cdot O \cdot CO \cdot Cl$, is formed; it can be obtained as a liquid by removing the toluene under reduced pressure, but cannot be distilled because it decomposes into benzyl chloride and carbon dioxide. It reacts in alkaline solution with the amino group of practically all amino-acids and peptides, whatever other groups they may contain, to give the so-called carbo-benzoxy derivative, the benzyl ester of a substituted urethane (p. 272):

$$H_2N \cdot R \cdot CO_2H \longrightarrow \phi CH_2 \cdot O \cdot CO \cdot NH \cdot R \cdot CO_2H.$$

The peculiar virtue of the carbo-benzoxy group for protecting an amino group is that for its removal hydrolysis is not needed; when a carbo-benzoxy derivative is reduced catalytically with hydrogen and palladium, the free amine, toluene, and carbon dioxide are formed:

$$\phi CH_2 \cdot O \cdot CO \cdot NH \cdot R \cdot CO_2H \longrightarrow \phi CH_3 + CO_2 + H_2N \cdot R \cdot CO_2H.$$
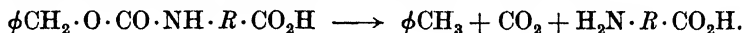
This fact makes the carbo-benzoxy group the most useful protecting group known and makes it possible to synthesize many peptides unobtainable by other methods.

Other devices have been used in particular instances which cannot be discussed here: one of them is referred to later (p. 371).

These problems of peptide synthesis have their counterpart in the problems of peptide degradation. The constitution of a naturally occurring peptide can be investigated by hydrolysis to the constituent amino-acids and identification of these, but even when this has been carried out, there still remains the question of the order of the amino-acids in the peptide chain. The free amino group of a simple peptide can be labelled by acylating it with benzoyl chloride or naphthalene sulphonyl chloride, and detecting which amino-acid is carrying the acyl group after hydrolysis of the peptide; this procedure can, however, only give a complete answer in the case of a dipeptide. M. Bergmann and L. Servas[2] have devised a combination of their carbo-benzoxy hydrogenation and Curtius's degradation of acid azides, by which the problem is solved and the amino-acids can be split off from a peptide chain one by one and identified. The method will be illustrated by the example of glycyl-alanyl-leucine. The free amino group is protected by benzoylation, and the benzoyl peptide converted into its azide through the ester and hydrazide (p. 398). When the azide is warmed with benzyl alcohol, it loses nitrogen and rearranges to an isocyanate (p. 375), which unites with the alcohol to give the carbo-benzoxy derivative. This is hydrogenated; the product is an acyl derivative of a diamine in which both amino groups are attached to one carbon atom; when treated with water it undergoes hydrolysis to give an aldehyde

[1] *Ber.* 1932, **65**, 1192: an interesting article on the applications of the carbo-benzoxy method is by M. Bergmann, *Science*, 1934, **79**, 439.

[2] *J. biol. Chem.* 1936, **113**, 341.

and the amide of a peptide with one less amino-acid residue. Identification of the aldehyde by some suitable derivative identifies the terminal amino-acid residue, and the process can be repeated.

$$-R \cdot CO \cdot NH \cdot CHR' \cdot COOH$$
$$\downarrow$$
$$-R \cdot CO \cdot NH \cdot CHR' \cdot CON_3$$
$$\downarrow$$
$$-R \cdot CO \cdot NH \cdot CHR' \cdot NH \cdot CO \cdot O \cdot CH_2\phi$$
$$\downarrow$$
$$-R \cdot CO \cdot NH \cdot CHR' \cdot NH_2 + CO_2 + CH_3\phi$$
$$\downarrow$$
$$-R \cdot CO \cdot NH_2 + R'CHO + NH_3$$
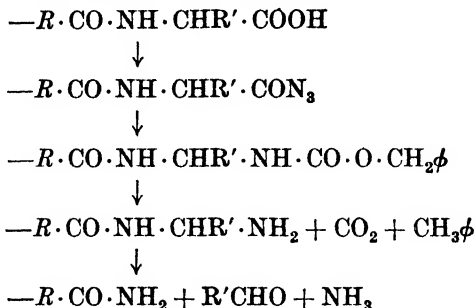
The essential step in this beautiful method is that the aldehyde is split off under conditions which do not suffice for the hydrolysis of the remaining peptide links. For the tripeptide named above we have:

Benzoyl-glycyl-alanyl-leucine
$$\downarrow$$
Benzoyl-glycyl-alanine + isovaleric aldehyde
$$\downarrow$$
Benzoyl-glycine + acetaldehyde.
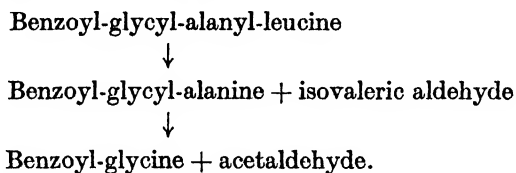
The physical properties of the peptides resemble those of the amino-acids in many respects. They are colourless micro-crystalline powders, mostly soluble in water, but not in alcohol or acetone, and decompose indistinctly at 200–250°. In view of the fact that they contain free amino and carboxyl groups, this is hardly surprising, and indicates that they exist as zwitterions. Those of higher molecular weight are less soluble in water, and are precipitated from solution by saturation with ammonium sulphate, or by addition of phosphotungstic acid. Their properties resemble those of the proteoses and peptones which are obtained by the partial hydrolysis of proteins; of these the former are precipitated by ammonium sulphate, but not the latter.

There is no doubt whatever that the peptide link is present in the proteins. A large number of polypeptides are hydrolysed to amino-acids by the same enzymes which bring about the complete hydrolysis of proteins, and many peptides which have been prepared by synthesis have proved to be identical with the compounds obtained by carefully regulated partial hydrolysis of proteins. The problem of isolating individual compounds from the complex mixtures formed is, of course, one of extreme difficulty because of the properties of the peptides. Success has, however, been achieved in some instances; for example, Abderhalden[1] hydrolysed silk with 70 per cent. sulphuric acid at 26°, and from the product obtained glycyl-*l*-tyrosine and *d*-alanyl-glycine in a crystalline state. More often in

[1] Z. physiol. Chem. 1909, **63**, 401; **64**, 436.

such experiments dipeptides are obtained not as such, but as their anhydrides, diketo-piperazine derivatives. These anhydrides are readily formed from dipeptides during the operations used in separating the mixture:

$$
\begin{array}{c}
R \\
| \\
CH-CO_2H \\
NH \\
| \\
CO \\
CH-NH_2 \\
| \\
R'
\end{array}
\longrightarrow
\begin{array}{c}
R \\
| \\
CH \\
NH \quad CO \\
| \qquad | \\
CO \quad NH \\
CH \\
| \\
R'
\end{array}
+ H_2O.
$$
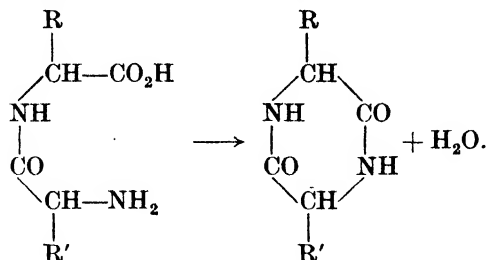
It was thought at one time that such diketo-piperazine structures might be present in the protein itself. This possibility can be ruled out; no case is known in which a compound of this structure is hydrolysed under physiological conditions by any of the most important of the protein-splitting enzymes.[1] Another clear indication that the diketo-piperazine structure is of little importance for the linkage of amino-acids in proteins is afforded by the work of M. Bergmann, L. Servas, and H. Köster.[2] Clupein is a protamine which can be obtained from the herring; it contains arginine, and it is known that the guanidine residue of arginine is not involved in the linkage to the rest of the protamine molecule. The arginine must then be held either in a diketo-piperazine or in a peptide linking.

$$
\begin{array}{cc}
CH_2\cdot CH_2\cdot CH_2\cdot CH-CO & \qquad CH_2\cdot CH_2\cdot CH_2\cdot CH\cdot CO_2H \\
| \qquad\qquad | \quad | & \qquad\qquad | \qquad\qquad\qquad | \\
NH \qquad\quad NH \; NH & \qquad NH \qquad\qquad\qquad NH \\
| \qquad\qquad\quad | \quad | & \qquad\qquad | \qquad\qquad\qquad | \\
C{:}NH \qquad\quad CO-CH\cdot R & \qquad C{:}NH \qquad\qquad\quad CO\cdot CHR\cdot NH_2 \\
| & \qquad\qquad | \\
NH_2 & \qquad\qquad NH_2
\end{array}
$$
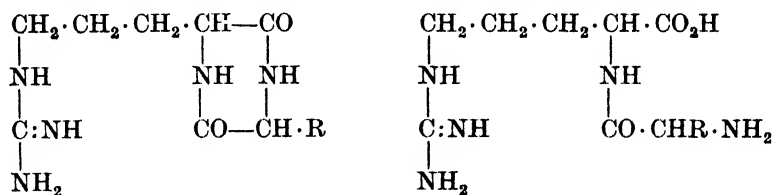
It was found that optically active compounds of the first type (the molecule contains two asymmetric carbon atoms) racemize at room temperature in presence of alkali in 45–60 minutes, while dipeptides of the second type show no racemization even after long periods of time. Clupein itself is not racemized by alkali, and hence it is very unlikely to contain diketo-piperazine units. For these reasons the isolation of diketo-piperazines from the hydrolysis products of proteins can be taken as further evidence of the existence of polypeptide chains in the proteins.

The description of the proteins and the discussion of the many problems which their structure presents lie outside the scope of this book. The molecular weight of typical proteins is much greater than that of any synthetic polypeptide; that of egg albumen has been measured by three independent methods, velocity of diffusion through a porous membrane,[3]

[1] E. Waldschmidt-Leitz, *Ber.* 1925, **58**, 1356; 1928, **60**, 359.

[2] Ibid. 1929, **62**, 1901.

[3] J. W. McBain, C. R. Dawson, and H. A. Barker, *J. Amer. C. S.* 1934, **56**, 1021.

osmotic pressure measurements,[1] and by sedimentation equilibrium and sedimentation velocity in the ultra-centrifuge.[2] All the methods agree and indicate that the molecular weight is of the order of 34,000. Hence any simple correspondence between synthetic polypeptides and proteins is hardly to be expected. The striking fact seems to emerge from molecular weight determinations on proteins that their molecules are simple multiples or submultiples of 34,000; this regularity seems to hold from the lowest molecular weight so far observed for a real protein (17,000) up to the highest (5,000,000).

There is a further reason why even the longest peptide chains known do not behave as proteins; all natural proteins on hydrolysis give considerable amounts of the diamino-monocarboxylic acids and of the monoamino-dicarboxylic acids, so that the main peptide chain of a protein must be carrying side-chains which terminate in amino or carboxyl groups. The synthetical polypeptides contain only the one free amino group and the one free carboxyl group at the ends of the chain, and this difference must be of great importance. Some of the carboxyl groups of a protein are present as amides ($—CO \cdot NH_2$); asparagine, the monoamide of aspartic acid, has been isolated from the products of enzyme hydrolysis of edestine,[3] and glutamine, the monoamide of glutamic acid, from gliadine;[4] ammonia coming from amide groups is formed in the hydrolysis of nearly all proteins. The side-chain amino and carboxyl groups of a protein might serve as starting-points for other peptide chains, so that the protein might have a branched structure; no one, however, has ever isolated a tripeptide fragment of such a structure as to prove the existence of a point of branching. Some of the amino and carboxyl groups are certainly free and can be detected and estimated in the same way as for amino-acids. Sörensen[5] has shown that if egg albumen is allotted a molecular weight of 34,000, the molecule must contain about 90 free carboxyl groups and an equal number of amino groups. The state in which these free groups exist will be governed by the same considerations as with the amino-acids, and there is every reason to suppose that the amino groups are $—NH_3^+$ and the carboxyl groups $—CO_2^-$; in other words the protein molecule must be a polyvalent zwitterion when it is at its iso-electric point. This conclusion is supported by measurements of the dielectric constant of solutions of the plant protein zein in 70 per cent. n-propyl alcohol.[6] Some of the phenomena observed in proteins must be due to their polyvalent zwitterion nature, and cannot be expected from the simpler polypeptides.

In conclusion it should be mentioned that the X-ray examination of

[1] S. P. L. Sörensen, *C.r. du Lab. Carlsberg*, 1917, **12**, 262.

[2] A good account of this method by T. Svedberg will be found in *Science*, 1934, **79**, 327.

[3] M. Damodaran, *Biochem. J.* 1932, **26**, 235.

[4] M. Damodaran, G. Jaaback, and A. C. Chibnall, ibid. 1704.

[5] S. P. L. Sörensen, K. Linderström-Lang, and E. Lund, *J. gen. Physiol.* 1927, **8**, 543.

[6] J. Wyman, *J. biol. Chem.* 1931, **90**, 443.

those proteins which occur as fibres, such as silk and hair, provides valuable confirmatory evidence of the repetition of the peptide link in proteins. Such proteins consist of long polypeptide molecules having a repeating unit, which is

$$\diagup NH \diagdown_{CH} \diagup CO \diagdown$$
$$\underset{R}{\overset{|}{}}$$
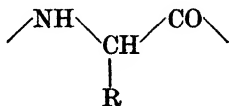
the remainder of the constituent amino-acid molecules forming lateral extensions.[1] The further question as to whether in a protein the various constituent amino-acids are arranged in a regular order along the peptide chain is more difficult to answer. Bergmann[2] has, however, pointed out that his very careful analysis of gelatine shows that it contains glycine, proline, and hydroxyproline in the simple molecular ratios of 6:3:2, and this fact supports the suggestion that these three amino-acids occupy a definite periodic position in the protein.

AROMATIC AMINO-ACIDS

The compounds which contain a carboxyl and an amino group directly attached to a benzene nucleus can be dismissed briefly. They are obtained by obvious modifications of the methods used for preparing aromatic amines and carboxylic acids. Their chemical properties offer few points of interest, and can be summarized in the statement that in general they behave as aromatic amines and as aromatic acids. The preparation of indigo from anthranilic acid is discussed later (p. 509).

The three simple benzene derivatives are:

	m.p.
o-Amino-benzoic acid, anthranilic acid	145°
m-Amino-benzoic acid	173°
p-Amino-benzoic acid	186°

They are somewhat soluble in water, easily soluble in alcohol and ether, and, with the exception of the meta acid, soluble in benzene; they can be sublimed without decomposition under reduced pressure. These properties are very different from those of the aliphatic amino-acids and suggest that in the solid state they do not exist as the zwitterions, $H_3^+N \cdot C_6H_4 \cdot CO_2^-$, but as the uncharged molecules, $H_2N \cdot C_6H_4 \cdot CO_2H$. This view is confirmed by the fact that in aqueous solution there is no great preponderance of zwitterions, but both states of the molecule are, at a rough estimate, equally probable. They show two dissociation constants in solution and Bjerrum[3] found that, whether these were interpreted on the assumption that the predominating form was the zwitterion, or that it was the uncharged molecule, values were obtained which agreed reasonably well with those to be expected. The same point is brought out

[1] Silk fibre: K. H. Meyer and H. Mark, *Ber.* 1928, **61**, 1932. Hair: with a discussion of its elasticity, W. T. Astbury and H. J. Woods, *Phil. Trans.* 1933, **232**, 333.
[2] *J. biol. Chem.* 1935, **110**, 471.   [3] *Z. phys. Chem.* 1923, **104**, 147.

clearly by measurements of heats of neutralization.[1] The main contribution to the heat of neutralization of a carboxylic acid is from the reaction $H^+ + OH^- \longrightarrow H_2O$, since the heat of dissociation of the carboxyl group $-CO_2H \longrightarrow -CO_2^- + H^+$ is small. Hence the heat of neutralization of a carboxylic acid is large. Neutralization of a zwitterion, however, involves the dissociation $-NH_3^+ \longrightarrow -NH_2 + H^+$, and this, as we have seen above, is an endothermic process and is accompanied by a large absorption of heat. Hence the heat of neutralization of glycine is 10,000 cals. smaller than that of acetic acid. The amino-benzoic acids show heats of neutralization which are only slightly smaller that that of benzoic acid, so that they cannot exist predominantly as zwitterions in aqueous solution. The meta acid gives the smallest heat and there must be a greater proportion of zwitterions in solutions of this acid than of the other two.

[1] G. Devoto, *Zent.* 1934, ii. 209; *Atti R. Accad. Lincei*, 1934, [6], **19**, 50.

AMIDES

AMIDES OF CARBOXYLIC ACIDS

THE characteristic group present in the simple carboxylic amides is
—CO·NH$_2$; they are the acyl substitution products of ammonia. In
addition to these there are the secondary amides (R·CO)$_2$NH and the
tertiary amides (R·CO)$_3$N. A marked distinction between the amides
and the amines is the ease with which the carbon-nitrogen link in the
former is broken by hydrolysis. The amides are only very weakly basic
and hence quaternary amides are unknown. The acyl derivatives of the
primary and secondary amines form the class of the N-substituted amides,
of which the anilides, of the general formula R·CO·NHϕ, are an important
example.

Many natural products are acid amides; urea (see Chapter IX), the di-
amide of carbonic acid, is the best-known example together with its cyclic
derivatives the pyrimidines and purines. The proteins and peptides are
mainly linear polyamide chains derived from the amino-acids (see p. 126).
The monoamides of the amino-acids, aspartic and glutamic acids, usually
called asparagine and glutamine, are essential constituents of plant-cell
sap. The pungent principles which give to many plants a pepper-like
taste are all N-substituted amides of unsaturated acids.[1] The alkaloids of
pepper, piperine and chavicine belong to this class as well as capsaicine
from red pepper and pellitorine from pyrethrum roots.[2]

Methods of Formation

1. The simple amides can often be obtained by heating the ammonium
salts of the acids:

$$R·CO_2NH_4 \longrightarrow R·CONH_2 + H_2O.$$

It was by heating ammonium oxalate that J. B. A. Dumas in 1830 pre-
pared oxamide, the first known amide. The ammonium salt cannot be
made in most cases by evaporating the aqueous solution, because being
the salt of a weak acid with a weak base, it is hydrolysed in solution and
the ammonia distils off with the water vapour. It is best made by passing
ammonia into the liquid anhydrous acid or adding ammonium carbonate
to the acid, or a mixture of the sodium salt and ammonium chloride can
be employed. Good yields of the amide can often be obtained by heating
the salt alone, if the right temperature (usually about 170–200°) and

[1] H. Staudinger and H. Schmeider, *Ber.* 1923, **56**, 699; H. Staudinger and F.
Müller, ibid., p. 711; E. Ott and K. Zimmermann, *Annalen*, 1921, **425**, 314; E. C. S.
Jones and F. L. Pyman, *J.C.S.* 1925, **127**, 2588.

[2] J. M. Gulland and G. U. Hopton, *J.C.S.* 1930, 6.

duration of heating are chosen.[1] Alternatively, an inert high-boiling solvent such as nitrobenzene can be used in which the salt is suspended, or the salt can be heated in a sealed tube, in which case the conversion is usually not complete because the water formed cannot escape and an equilibrium is set up. Sometimes excess of the acid is used as a solvent. Acetamide is best made by boiling a solution of ammonium acetate in glacial acetic acid under a reflux air condenser and allowing the acid to distil over slowly: the water formed distils with it and is thus removed. The acetamide, which like all amides boils at a much higher temperature than the acid from which it is derived, is separated from the excess acid by distillation. A similar method can be used for the preparation of acetanilide from glacial acetic acid and aniline. Formanilide, $H \cdot CONH\phi$, is produced very readily, even if dilute formic acid is boiled with aniline. H. Goldschmidt and his pupils[2] have measured the rate of formation of anilides from fatty acids in the presence of excess of the aromatic amine, and have found that for the different acids the velocities with any amine are approximately in the ratios:

Formic	*Acetic*	*Propionic*	*Butyric*	*Isobutyric*
1,000	1	0·5	0·3	0·1

This method of formation is formally analogous to the esterification of an acid:

$$R \cdot C\underset{\diagdown OH}{\overset{\diagup O}{}} + HNH_2 \longrightarrow R \cdot C\underset{\diagdown NH_2}{\overset{\diagup O}{}}$$

$$R \cdot C\underset{\diagdown OH}{\overset{\diagup O}{}} + HOEt \longrightarrow R \cdot C\underset{\diagdown OEt}{\overset{\diagup O}{}}$$
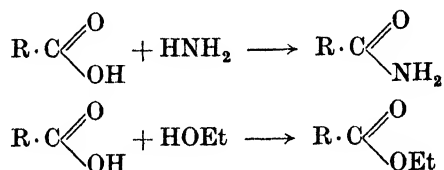
The kinetics of the two reactions are somewhat similar, in that both reactions are reversible and catalysed to a large extent by the hydrogen ion.[3]

2. Amides may be prepared by the action of ammonia on esters. By this method Liebig obtained oxamide from ethyl oxalate in 1834: in this case the reaction proceeds extremely rapidly at room temperature:

$$EtO_2C \cdot CO_2Et + 2NH_3 \longrightarrow NH_2 \cdot CO \cdot CO \cdot NH_2 + 2EtOH.$$

The best yields are obtained by shaking the ester in the cold with concentrated aqueous ammonia, or, in the case of an insoluble ester, by treating it with alcoholic ammonia, sometimes at higher temperatures. The reaction does not proceed in the absence of water,[4] and is subject to what may be steric effects. Thus ethyl monoalkylmalonates react less readily than diethyl malonate, and diethyl dialkylmalonates react with

[1] H. Decker, *Annalen*, 1913, **395**, 282.
[2] H. Goldschmidt and C. Wachs, *Z. phys. Chem.* 1897, **24**, 353; H. Goldschmidt and R. Braüer, *Ber.* 1906, **39**, 97.
[3] H. Goldschmidt and C. Wachs, *Z. phys. Chem.* 1897, **24**, 353.
[4] G. H. Grant and C. N. Hinshelwood, *J.C.S.* 1933, 1351.

great difficulty or not at all, though the corresponding dimethyl esters yield diamides in these cases. The nature of the acid also seems to have a great influence on the ease with which the reaction proceeds: the esters of trimethylacetic acid do not react with ammonia,[1] while those of trichloracetic acid react very readily.

3. A general method for obtaining amides and N-substituted amides is the action of ammonia, or a primary or secondary amine, on the acid chloride or anhydride:

$$R \cdot COCl + R \cdot NH_2 \longrightarrow R \cdot CO \cdot NHR + HCl$$
$$(R \cdot CO)_2O + R \cdot NH_2 \longrightarrow R \cdot CO \cdot NHR + R \cdot CO_2H.$$
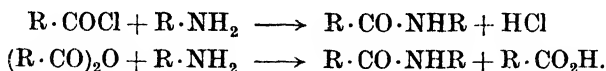
The acid chloride, and not the anhydride, is generally used. Acetic anhydride is, however, a commercial product, so that substituted acetamides are prepared by treating primary or secondary amines with it. The first amide prepared by this general method was benzamide which J. Liebig and F. Wöhler obtained in 1832 by the action of ammonia on benzoyl chloride. With amides insoluble in water the acid chloride is usually poured into excess of aqueous ammonia to which crushed ice has been added. Anilides can be obtained similarly if the aqueous ammonia is replaced by aniline. An amide is often formed in good yield by passing dry ammonia through a solution of the acid chloride in benzene or chloroform: after the reaction, water is added to dissolve the ammonium chloride formed and the amide recovered from the organic solvent. To obtain N-substituted amides the amine can often be dissolved in pyridine and the acid chloride added: the reaction is very rapid and the amide, if insoluble in water, can be obtained by pouring the reaction mixture into water. In other cases dry acetone is a suitable solvent, solid potassium carbonate being added to absorb the hydrogen chloride formed. The so-called Schotten-Baumann reaction is an example of this method; primary and secondary higher amines and aromatic amines are often converted into their benzoyl derivatives, which are N-substituted benzamides, for purposes of identification or separation. This is usually carried out by suspending the amine in dilute aqueous caustic soda and adding benzoyl chloride a little at a time with vigorous shaking at room temperature.

The kinetics of the interaction of various substituted benzoyl chlorides with substituted anilines have been studied by Hinshelwood and his pupils with interesting results.[2] They used as solvents carbon tetrachloride, hexane, and benzene, in which the aniline hydrochloride resulting from the reaction is insoluble; the velocity of reaction could thus be followed by filtering off the precipitated hydrochloride and, after washing, determining its amount by volumetric estimation of chloride. The reaction is bimolecular,

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[1] H. Meyer, *Monats.* 1906, **27**, 31.

[2] G. H. Grant and C. N. Hinshelwood, *J.C.S.* 1933, 1351; E. G. Williams and Hinshelwood, ibid. 1934, 1079; W. B. S. Newling, L. A. K. Staveley, and Hinshelwood, *Trans. Faraday Soc.* 1934, **30**, 597.

but in the first two solvents, and especially in hexane, the homogeneous reaction is accompanied by a heterogeneous reaction which takes place on the surface of the precipitated amine hydrochloride, so that the reaction is autocatalytic and the velocity constants are anomalous. In benzene the homogeneous reaction is much faster than in the other solvents and outweighs the heterogeneous reaction almost entirely, so that it is more strictly bimolecular. The reaction belongs to that strange class where the measured rate is much smaller than the rate of collision of molecules containing sufficient energy to react; only a fraction of the collisions between molecules with the necessary energy content result in reaction. For anilide formation the fraction is of the order of 10^{-7}. The introduction of substituents into either of the two reactants brings about large changes in the rate of reaction, and in directions that would be expected. Thus p-toluidine reacts with benzoyl chloride about four times as fast as aniline, but m-nitroaniline reacts about 162 times as slowly as aniline: on the other hand, introduction of a substituent such as the nitro group into the acid chloride increases the rate, and that of a methyl group decreases it. The point of interest that emerges is that it was found by measurement of the temperature coefficients of these reaction velocities that the effect of substituents is solely on the energy of activation, i.e. on the energy a molecule must possess before it is capable of reacting, and that in all cases the fraction of collisions which are fruitful (10^{-7}) remains about the same. There are still some other conditions that must be satisfied for reaction to occur, which are unchanged by the introduction of substituents of the most diverse nature.

4. Amides are formed by the partial hydrolysis of the nitriles:

$$R \cdot C \equiv N + H_2O \longrightarrow R \cdot CONH_2.$$
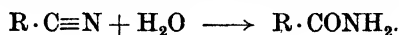
This can be effected by dissolving the nitrile in cold concentrated sulphuric acid and pouring into water, or by shaking with strong hydrochloric acid. It is sometimes, however, most easily carried out by a curious reaction, the action of hydrogen peroxide on the nitrile in alkaline solution:[1]

$$R \cdot CN + 2H_2O_2 \longrightarrow R \cdot CONH_2 + O_2 + H_2O.$$

The reaction is not a general one and fails with many nitriles,[2] so that the method is not of great preparative importance. A certain amount of light is thrown on the mechanism of the reaction whereby sulphuric acid converts a nitrile into an amide by the observations of A. Hantzsch.[3] He found that the ultra-violet absorption of a solution of p-tolyl cyanide, $CH_3 \cdot C_6H_4 \cdot CN$, in concentrated sulphuric acid altered with time and finally became identical with that of p-toluic amide in sulphuric acid. The rate of change of the absorption became smaller in the mixture $H_2SO_4 + H_2O$, yet smaller in the mixture $H_2SO_4 + 2H_2O$, and practically zero in the mixture $H_2SO_4 + 4H_2O$. It thus appears that the primary action is union between the nitrile and the acid to give a salt $[R \cdot C \colon NH]SO_4H$

[1] B. Radziszewski, *Ber.* 1885, **18**, 355.
[2] J. Deinert, *J. pr. Chem.* 1895, **52**, 431.   [3] *Ber.* 1931, **64**, 674.

which can react with the 0·2 per cent. of water in concentrated sulphuric acid to form the salt of the amide $[R \cdot C(OH):NH_2]SO_4H$; the presence of much water stops the reaction because the sulphuric acid then combines preferentially with the water, the nitrile being an extremely weak base. He showed that the heat of hydration of sulphuric acid is much greater than its heat of combination with the nitrile. The reaction also takes place in completely anhydrous sulphuric acid, and quite rapidly; in this case the nitrile salt must combine with another molecule of acid to give a compound of the type $[R \cdot C(O \cdot SO_2 \cdot OH):NH_2]SO_4H$, which is rapidly hydrolysed to the amide when the mixture is poured into water.

Formamide, the simplest amide, is best prepared by the partial hydrolysis of prussic acid.[1] If liquid hydrogen cyanide is mixed with sulphuric acid monohydrate, the acid sulphate of formamide $H \cdot CONH_2, H_2SO_4$ slowly crystallizes out: the reaction is catalysed by the presence of bromides or chlorides. The amide cannot be obtained from the salt by neutralization with aqueous alkalis, because formamide is so easily hydrolysed in the presence of water to formic acid and ammonia. It can be obtained, however, by covering the acid sulphate with dry ether and passing in dry ammonia to combine with the acid. It is best purified by distillation in a high vacuum.

Other reactions in which N-substituted amides are formed are the action of acids on the esters of isocyanic acid:

$$CH_3 \cdot CO_2H + EtN:C:O \longrightarrow CH_3 \cdot CO \cdot NHEt + CO_2$$
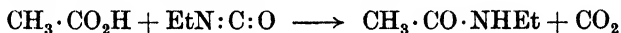
and the Beckmann rearrangement of ketoximes (see p. 177). Isocyanides when heated with a fatty acid give substituted formamides:

$$R \cdot NC + 2CH_3 \cdot CO_2H \longrightarrow H \cdot CO \cdot NHR + (CH_3 \cdot CO)_2O.$$
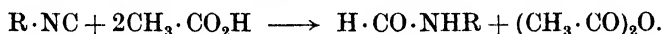
The secondary and tertiary amides are best obtained by boiling the primary amides or nitriles with an acid anhydride, or by treating the primary amide with an acid chloride in benzene solution, a method which is useful for preparing mixed secondary amides:

$$CH_3 \cdot CONH_2 + (CH_3CO)_2O \longrightarrow CH_3 \cdot CO \cdot NH \cdot CO \cdot CH_3 + CH_3 \cdot CO_2H$$

$$CH_3 \cdot CN + (CH_3CO)_2O \longrightarrow (CH_3 \cdot CO)_3N$$

$$CH_3 \cdot CONH_2 + R \cdot COCl \longrightarrow CH_3 \cdot CO \cdot NH \cdot CO \cdot R + HCl.$$
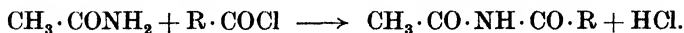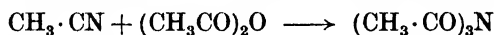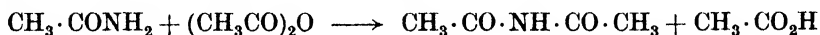
Secondary amides are also formed by heating a nitrile with an acid:

$$CH_3 \cdot CN + CH_3 \cdot CO_2H \longrightarrow CH_3 \cdot CO \cdot NH \cdot CO \cdot CH_3.$$
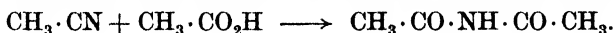
Their potassium derivatives result from the action of an acid anhydride on potassium cyanate:[2]

$$(CH_3 \cdot CO)_2O + KNCO \longrightarrow (CH_3CO)_2NK + CO_2,$$

and their alkyl derivatives from the action of anhydrides on isocyanic alkyl esters:

$$(CH_3CO)_2O + EtNCO \longrightarrow (CH_3CO)_2NEt + CO_2.$$
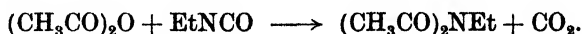
[1] P. L. Magill, *Ind. Eng. Chem.* 1934, **26**, 611.   [2] K. Brunner, *Ber.* 1914, **47**, 2671.

If acetamide is treated with metallic sodium in hot benzene, ammonia and hydrogen are evolved and the sodium derivative of diacetamide crystallizes out.[1] The sodium derivative of acetamide is first formed and reacts with another molecule of acetamide:

$$CH_3 \cdot CO \cdot NH_2 \longrightarrow CH_3 \cdot CO \cdot NHNa \xrightarrow{CH_3CONH_2} (CH_3 \cdot CO)_2NNa + NH_3.$$
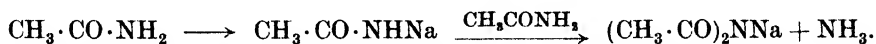
If potassium is used, only the first stage of the reaction takes place.

The amides are solids at room temperature, with the exception of formamide which melts at $2 \cdot 5°$. The lower members are very soluble in water and deliquescent; the amides of the simpler aromatic acids are less soluble in cold water, but quite soluble in hot water. The unpleasant smell associated with the simple aliphatic amides is due to impurities; acetamide as usually prepared smells like the excrement of mice, but the smell disappears after recrystallization from acetone. Most amides can be distilled without decomposition, and although an amine usually boils at a much lower temperature than the corresponding alcohol, the amides have much higher boiling-points than the acids from which they are derived.

MeOH .	.	b.p.$+65°$	H$\cdot CO_2$H .	.	b.p. $100 \cdot 6°$
MeNH$_2$.	.	,, $-6°$	H$\cdot$CONH$_2$	.	,, $122°/32$ mm.
EtOH .	.	,, $+78°$	Me$\cdot CO_2$H .	.	,, $118°$
EtNH$_2$.	.	,, $16 \cdot 5°$	Me$\cdot$CONH$_2$	.	,, $223°$
n-PrOH	.	,, $97°$	Et$\cdot CO_2$H .	.	,, $140°$
n-PrNH$_2$	.	,, $49°$	Et$\cdot$CONH$_2$	.	,, $213°$

This probably arises from the fact that the amides are associated in the liquid state; their association in solution, even in water, has been proved by A. N. Meldrum and W. E. S. Turner.[2] Formamide is exceptional in several ways. It decomposes at its boiling-point under atmospheric pressure into ammonia and carbon monoxide; it is both formed and hydrolysed more readily than other amides; and finally its dielectric constant is 84, which is greater than that of water. As a solvent it resembles water in some respects; many salts are readily soluble in it to give conducting solutions, and these solutions can be used for the electrodeposition of some metals.[3] On the other hand, a fairly strong acid such as tribromacetic acid is not ionized at all in formamide solution.[4] The salts of weak bases are 'amidolysed' in formamide just as they are hydrolysed in water; for example from a solution of antimony trichloride in formamide a white precipitate separates, which is a mixture of the compounds $SbCl_2X$, $SbClX_2$, and SbX_3, where $X = H \cdot CO \cdot NH-$. Formamide also resembles water in that almost every salt which will crystallize with water of crystallization will also combine with formamide.[5] These properties are shown, though not so markedly, by the other simple aliphatic amides.

[1] J. N. Rakshit, *J.C.S.* 1913, **103**, 1559.   [2] Ibid. 1908, **93**, 876.
[3] Magill, loc. cit.   [4] P. Walden, *Zent.* 1912, i, 122.
[5] B. Menschutkin, ibid. 1909, i, 909.

Acetamide is a remarkable solvent, capable of dissolving almost every class of compound.

The amides, in marked contrast to the amines, are very weak bases and only form salts with strong acids, and these are profoundly hydrolysed in aqueous solution. The hydrochloride of acetamide was found by J. K. Wood[1] to be hydrolysed to an extent of 91·3 per cent. in decinormal aqueous solution, which indicates that the basic dissociation constant of acetamide is of the order of 10^{-14}. Some amides form salts of an anomalous composition; thus the hydrochloride of acetamide loses hydrogen chloride and passes into a salt, $(CH_3 \cdot CONH_2)_2, HCl$, which is more stable and can be recrystallized from alcohol. There are indications that these anomalous salts can exist in aqueous solution in the presence of large excess of hydrogen chloride.[2] The N-alkyl amides are more strongly basic and form stable platinichlorides.

On the other hand, the amides show acidic properties and can give rise to salts with metals. If acetamide is heated with metallic potassium in benzene, hydrogen is evolved and potassium acetamide crystallizes out. A convenient method of obtaining such salts is by the interaction of an amide with sodamide or potassamide.[3] These salts are completely decomposed by water or alcohol. In liquid ammonia, which behaves in many ways like water, the amides are distinctly acidic and decolorize phenolphthalein which has been reddened by a trace of a base such as sodamide. E. C. Franklin has studied the 'ammonia' system of acids, bases, and salts, in which acid amides are the acids and alkali amides the bases, and in which neutralization reactions of the following type occur:

$$R \cdot CONH_2 + NaNH_2 \longrightarrow R \cdot CO \cdot NHNa + NH_3,$$

which is analogous to
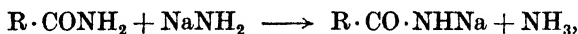
$$R \cdot CO_2H + NaOH \longrightarrow R \cdot CO_2Na + H_2O,$$
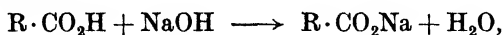
in water.[4] The secondary amides, such as diacetamide, $(MeCO)_2NH$, show no basic properties whatever,[5] but, as would be expected, their acidic character is more marked than that of the monoamides; the sodium salt of diacetamide is stable in alcoholic solution.[6] These secondary amides are, of course, similar to the imides of dibasic acids (see p. 152).

Aqueous solutions of most amides will dissolve mercuric oxide, and by evaporation the stable mercuric derivatives are obtained: that from benzamide has the formula $(\phi \cdot CONH)_2Hg$, and can be crystallized from hot caustic potash without any decomposition. These compounds are not true salts and their solutions show none of the characteristic reactions of

[1] *J.C.S.* 1903, **83**, 576.

[2] T. W. J. Taylor, ibid. 1930, 2741.

[3] A. W. Titherley, ibid. 1902, **81**, 1527.

[4] Summarizing paper, E. C. Franklin, *Amer. Chem. J.* 1912, **47**, 285. See also *The Nitrogen System of Compounds*, by E. C. Franklin, Amer. Chem. Soc. Monograph, No. 68, New York, 1935.

[5] W. Hentschel, *Ber.* 1890, **23**, 2395.   [6] J. N. Rakshit, *J.C.S.* 1916, **109**, 181.

the mercuric ion; the mercury is covalently linked, most probably to the nitrogen atoms.

The actual structure of the amide group and of its salts with acids and bases is by no means an easy problem to solve. There are three possibilities for the amide itself, the usually accepted formula (I), the so-called isoamide formula (II), and the betaine-like formula (III). The difference between (I) and (II) is a tautomeric difference, while that between (I)

$$\text{I. } R \cdot C \overset{\displaystyle O}{\underset{\displaystyle NH_2}{\diagdown}} \qquad \text{II. } R \cdot C \overset{\displaystyle OH}{\underset{\displaystyle NH}{\diagdown}} \qquad \text{III. } R \cdot C \overset{\displaystyle O^-}{\underset{\displaystyle NH_2^+}{\diagdown}}$$
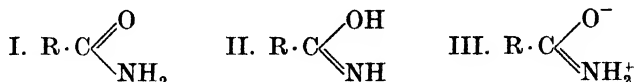
and (III) does not involve the shift of any atom, but only the arrangement of electrons. It is not impossible that any given amide can exist in all of these three forms according to the conditions of solvent and temperature, or it may be a resonance-hybrid derived from the forms (I) and (III). A. Hantzsch[1] has attempted to discover the form in which an amide exists in various solvents by comparing its ultra-violet absorption spectrum with those of its alkyl derivatives in which the two forms (I) and (II) are fixed by substitution of the hydrogen atoms by alkyl groups. The method cannot be applied to the simple aliphatic amides because they do not absorb in the ultra-violet, but trichloracetamide in solution in chloroform and aqueous methyl alcohol has an absorption which resembles that of the imino-ether, $CCl_3 \cdot C(OCH_3):NH$, more closely than that of the piperidine derivative, $CCl_3 \cdot CO \cdot NC_5H_{10}$, in which the true amide structure (I or III and not II) is fixed. Benzamide also in alcoholic solution has an absorption spectrum identical with that of the imino-ether, $\phi \cdot C(OEt):NH$, and unlike that of dimethylbenzamide, $\phi \cdot CO \cdot NMe_2$. The evidence seems conclusive in these cases, but whether the conclusion should be extended to all amides is not known. Similarly, comparison of the ultra-violet absorption spectra of acetanilide with those of its N-alkyl derivatives such as $Me \cdot CO \cdot N\phi Me$, shows that there is little resemblance, and indicates that the anilide should be written $Me \cdot C(OH):N\phi$.[2] Hantzsch has also suggested that the strong association of the amides arises from the hydroxyl groups of formula (II), and has pointed out that the boiling-point of an amide is lowered by the successive introduction of alkyl groups:

$$\begin{array}{llllll}
CH_3 \cdot CO \cdot NH_2 & . & . & . & . & \text{b.p. } 223^\circ \\
CH_3 \cdot CO \cdot NHMe & . & . & . & . & \text{,, } 206^\circ \\
CH_3 \cdot CO \cdot NMe_2 & . & . & . & . & \text{,, } 166^\circ
\end{array}$$

Since, however, the actual mechanism of association between amide molecules is unknown, this cannot be held as evidence of the imino-hydrin structure (II).

On the other hand, the heats of formation of formamide and acetamide from their elements are greater than would be expected from the linkings

[1] *Ber.* 1931, **64**, 661.

[2] P. Ramart-Lucas and P. Wohl, *C.r.* 1933, **196**, 120.

the molecules contain, and L. Pauling and J. Sherman[1] interpret this as an indication of resonance between the structures (I) and (III). Aqueous solutions of formamide have a dielectric constant larger than that of water, a property shown also by amino-acids and urea which are known to have a zwitterion structure; this may be evidence for a similar structure (III) for formamide. In the gaseous state formamide shows neither the characteristic infra-red absorption of the $\rangle C=O$ group, nor that of the —NH_2 group,[2] which also seems to exclude formula (I) in this case. Formamide is, however, exceptional in several ways, and its property of increasing the dielectric constant of water is not shown by any other amide.[3]

The structure of the salts formed with acids is, perhaps, a little more certain. There are two possibilities:

$$\text{IV. } R \cdot C \Big\langle \begin{matrix} OH \\ NH_3^+ \end{matrix} \ [X] \qquad \text{V. } R \cdot C \Big\langle \begin{matrix} O \\ NH_3^+ \end{matrix} \ [X]$$
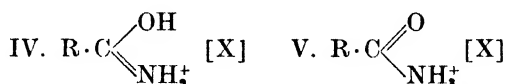
Of these (IV) is to be preferred, both by analogy with the salt formation of urea and thio-urea (see p. 284) and also as a consequence of Hantzsch's measurements[4] of the ultra-violet absorption of benzamide in strong sulphuric acid, which is identical with that of the imino-ether $\phi \cdot C(OEt):NH$ in the same solvent. This latter compound can only form a salt, $[\phi \cdot C(OEt):NH_2]X$. In the case of the metallic compounds of the amides which are true salts, there are again two possibilities:

$$\text{VI. } R \cdot C \Big\langle \begin{matrix} O^- \\ NH \end{matrix} \ [Na] \qquad \text{VII. } R \cdot C \Big\langle \begin{matrix} O \\ NH^- \end{matrix} \ [Na]$$
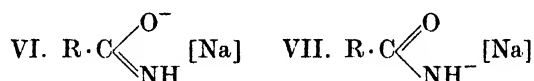
but there is no difference between these two formulations of the anion except in the position of electrons, and hence it is extremely unlikely that two separate compounds can exist. Formula (VI) is the more likely structure for the anion; these salts react with alkyl halides to give O-alkyl and not N-alkyl compounds, and this supports formula (VI), although evidence of this nature is notoriously untrustworthy. Some of the metallic derivatives, especially the mercuric compound, are not true salts, and in these, two distinct compounds might exist, but no certain case of this isomerism is known.

Reactions of the Amides

A marked difference between amides and amines is the ease with which the carbon-nitrogen bond in the former can be broken by hydrolysis. The reaction between an acid and ammonia to give an amide and water is reversible and an amide can be hydrolysed to the acid slowly by heating

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[1] *J. chem. Physics*, 1933, **1**, 609.

[2] G. Herzberg and R. Kölsch, *Z. Elektrochem.* 1933, **39**, 573.

[3] G. Devoto, *Gazz.* 1932, **61**, 897.   [4] Loc. cit., p. 673.

with water. The hydrolysis is much more rapid in the presence of the hydrogen or hydroxyl ion:

$$R \cdot CONH_2 + H_3O^+ \longrightarrow R \cdot CO_2H + NH_4^+$$
$$R \cdot CONH_2 + OH^- \longrightarrow R \cdot CO_2^- + NH_3.$$
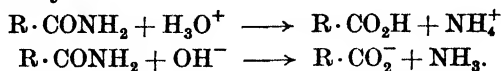
Certain amides can only be hydrolysed with difficulty, notably aromatic amides in which one or both positions ortho to the amide group are filled by substituents. This is one of the classical cases of steric hindrance. In such cases the hydrolysis can usually be effected by heating to 150° with anhydrous orthophosphoric acid.[1] The rate of hydrolysis of acetamide and of benzamide by acids and alkalis has been measured.[2] Caustic alkalis give velocity constants about seven times as large as mineral acids at an equivalent concentration. In dilute solution the rate is proportional to the concentration of the catalytically active ion. The velocity of hydrolysis of acetamide with hydrochloric acid has, however, a maximum value when the acid is 3N; at higher strengths the velocity falls off rapidly. This curious effect seems to be due to the formation of a salt of the amide in the presence of the large excess of acid, the salt being incapable of hydrolysis.[3] Amides can also be hydrolysed by enzymes such as pepsin. Under ordinary laboratory conditions amides are unattacked by alcohols, and they are, in fact, frequently crystallized from alcohol or dilute alcohol. However, at temperatures above 200° amides are slowly converted by alcohols into esters and ammonia: $R \cdot CONH_2 + R'OH \rightarrow R \cdot CO_2R' + NH_3$.

They react with nitrous acid, but only in the presence of a mineral acid, to give a quantitative yield of nitrogen and the acid:

$$R \cdot CONH_2 + HNO_2 \longrightarrow R \cdot CO_2H + N_2 + H_2O.$$
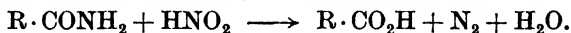
On reduction with sodium and alcohol amides are converted sometimes into a primary amine, $R \cdot CH_2 \cdot NH_2$, and sometimes into the related primary alcohol, $R \cdot CH_2 \cdot OH$, the nitrogen being lost as ammonia. Catalytic reduction with hydrogen gives the amine, but a solvent such as dioxane must be used to reduce the concentration of the water formed and avoid hydrolysis of the amide.[4] Amides can be dehydrated to the corresponding nitrile by agents such as phosphorus pentoxide or pentachloride, or, best of all, thionyl chloride. Formamide is converted into hydrocyanic acid and water by passing its vapour over thoria or pumice at 400°. Thus the interconversion of ammonium salt, amide, and nitrile is reversible:

$$CH_3 \cdot CO_2NH_4 \underset{H_2O}{\overset{heat}{\rightleftharpoons}} CH_3 \cdot CONH_2 \underset{H_2SO_4 \; or \; H_2O_2}{\overset{SOCl_2}{\rightleftharpoons}} CH_3 \cdot CN.$$

[1] G. Berger and S. C. J. Olivier, *Rec. trav. chim.* 1927, **46**, 600; Olivier, ibid. 1929, **48**, 568.

[2] N. von Peskoff and J. Meyer, *Z. phys. Chem.* 1913, **82**, 129; J. C. Crocker, *J.C.S.* 1907, **91**, 593; S. Kilpi, *Z. phys. Chem.* 1912, **80**, 165; I. Bolin, *Z. anorg. Chem.* 1925, **143**, 210; H. v. Euler and A. Ölander, *Z. phys. Chem.* 1928, **131**, 107; T. W. J. Taylor, *J.C.S.* 1930, 2741. [3] Taylor, loc. cit.

[4] B. Wojcik and H. Adkins, *J. Amer. C. S.* 1934, **56**, 2419.

The most certain way of distinguishing the presence of a carboxyl group in an acidic substance of unknown constitution from any other acidic group such as a strongly acidic phenolic group is to convert successively into the acid chloride, the amide, and the nitrile.

An important reaction of amides is their conversion into amines containing one carbon atom less, known as the Hofmann reaction:

$$R \cdot CONH_2 \longrightarrow R \cdot NH_2.$$

The reagents are bromine and alkali, or sometimes, especially on the technical scale, chlorine and alkali. The intermediate stages of the reaction are well established. The amide is first converted into the monobromamide, $R \cdot CO \cdot NHBr$, which, as Hantzsch showed,[1] is a pseudo-acid and forms with the alkali a salt of the isoamide structure

$$R \cdot C \underset{NBr}{\overset{O^-}{\diagup}} [Na].$$
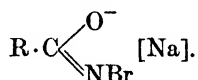
This salt contains the system $\diagup C{=}N{-}$, and on heating in alkaline solution undergoes a rearrangement very similar to the rearrangements of other compounds containing that system, i.e. the Beckmann rearrangement of the oximes (p. 177), and the Curtius degradation of the azides (p. 375).

$$R \cdot \underset{NBr}{\overset{\|}{C}} {-} O^- \longrightarrow Br \cdot \underset{N \cdot R}{\overset{\|}{C}} {-} O^- \longrightarrow R \cdot N{:}C{:}O + NaBr$$
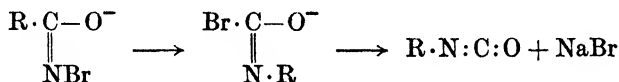
The alkali bromide is simultaneously lost and an isocyanate results: this can be obtained by steam distillation of the reaction mixture, if only one equivalent of alkali is used.[2] Under normal conditions excess alkali is present and the isocyanate is hydrolysed to the amine and carbon dioxide:

$$R \cdot N{:}C{:}O + H_2O \longrightarrow R \cdot NH_2 + CO_2.$$
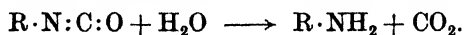
At the same time, and especially if the alkali is not in excess, the amine reacts with unhydrolysed isocyanate to give the urea $CO(NHR)_2$.

The mechanism of the rearrangement that takes place in the Hofmann reaction has been the subject of much discussion. J. Stieglitz[3] suggested that the salt of the bromamide lost potassium bromide to form a radical containing monovalent nitrogen which passed into the isocyanate by migration of the hydrocarbon residue. There is a good analogy for this in

$$R \cdot C \underset{NBr}{\overset{OK}{\diagup}} \longrightarrow R \cdot C \underset{N}{\overset{O}{\diagup}} \longrightarrow O{:}C{:}N \cdot R$$
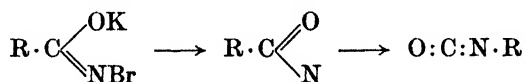
the decomposition of the azide of benzoic acid into phenyl isocyanate.[4]

$$\phi \cdot CO \cdot N_3 \longrightarrow N_2 + \phi \cdot CO \cdot N{\diagup} \longrightarrow \phi \cdot NCO$$
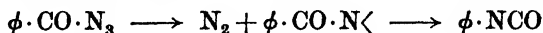
[1] *Ber.* 1902, **35**, 226, 3379.
[2] E. Mohr, *J. pr. Chem.* 1905, **72**, 297; 1906, **73**, 177, 228.
[3] *Amer. Chem. J.* 1896, **18**, 751; 1903, **29**, 49; *J. Amer. C. S.* 1914, **36**, 272.
[4] G. Schroeter, *Ber.* 1909, **42**, 2339.

The weakness of such an explanation is that it cannot be extended to the very similar Beckmann rearrangement of an oxime. In any event there is good evidence that there is no temporary detachment of the group R from the rest of the molecule during the rearrangement. E. S. Wallis and W. W. Moyer[1] studied the Hofmann reaction with the optically active form of the amide of 3,5-dinitro-6-α-naphthyl-benzoic acid. The activity is not due to the presence of any asymmetric atom, but to the fact that rotation
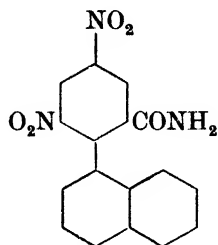
about the bond uniting the phenyl and naphthyl nuclei is prevented by the steric interference of the nitro and amide groups with the carbon atom of the second benzene nucleus of the naphthyl group (atropic enantiomorphism). The molecule is thus held in one configuration and is enantiomorphous: if the blocking effect of the groups ortho to the benzene-naphthalene link is removed, free rotation about that link is possible and the enantiomorphism disappears, because one configuration can be converted into the antimeric configuration by that rotation. It is known that removal of one of the ortho groups is sufficient to permit free rotation. Hence in the rearrangement of this amide to the amine if the migratory radical is detached from the rest of the molecule, the resulting amine should be optically inactive. It was found, however, to be optically active, and there seems to be no racemization whatever. Hence it must be concluded that the rearrangement of the amide $R \cdot CONH_2$ to the amine RNH_2 is entirely an intramolecular process which does not involve the temporary existence of the radical R.

An interesting modification of the Hofmann reaction is that of R. A. Weermann.[2] If the amide of an α-hydroxy acid is treated with sodium hypobromite or hypochlorite, sodium cyanate and an aldehyde are formed:

$$R \cdot CH(OH) \cdot CONH_2 \longrightarrow R \cdot CH(OH) \cdot N:CO \longrightarrow R \cdot CHO + HNCO.$$

Thus mandelic amide, $\phi CH(OH) \cdot CONH_2$, gives benzaldehyde. The reaction can be used to convert a hexose into a pentose: the hexose is oxidized to the hexonic acid, the lactone of which readily gives the amide on treatment with dry ammonia in alcohol; the amide is then treated with hypochlorite:

$$-CHOH \cdot CHO \longrightarrow -CHOH \cdot CO_2H \longrightarrow -CHO.$$

The formation of sodium cyanate when an amide is treated with sodium

[1] J. Amer. C. S. 1933, **55**, 2598.   [2] Rec. trav. chim. 1917, **37**, 16.

hypochlorite has also been used to diagnose the presence of an α-hydroxy group in an acid, as in certain derivatives of ascorbic acid (vitamin C).[1]

Cyclic amides formed by elimination of water between a carboxyl and an amino group in the same molecule are known as lactams. The name is derived from the analogy with the lactones which are formed by elimination of water from a carboxyl and a hydroxyl group in the same molecule. The ring-system is covalently linked and the ease of its formation is determined by the number of atoms separating the reacting groups. Thus glycine under no conditions gives a lactam, which would be a three-membered ring, but on dehydration gives a mixture of the dimolecular cyclic diketopiperazine and straight chain polymers of the polypeptide type:

$$H_2N \cdot CH_2 \cdot CO_2H \Bigg\langle \begin{array}{c} HN \Big\langle \begin{array}{c} CO\text{---}CH_2 \\ CH_2\text{---}CO \end{array} \Big\rangle NH \\ \\ H_2N \cdot CH_2 \cdot CO \cdot (NH \cdot CH_2 \cdot CO)_n NH \cdot CH_2 \cdot CO_2H. \end{array}$$
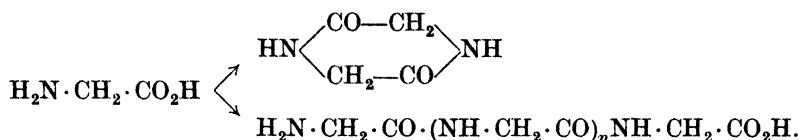
β-Aminopropionic acid (β-alanine) also shows no tendency to form the lactam, which would be a four-membered ring: on heating it loses ammonia to give acrylic acid:

$$H_2N \cdot CH_2 \cdot CH_2 \cdot CO_2H \longrightarrow CH_2 : CH \cdot CO_2H.$$
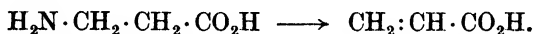
The next two higher acids give lactams quantitatively on heating: these contain five- and six-membered rings, respectively. The acid

$$H_2N \cdot (CH_2)_5 \cdot CO_2H$$
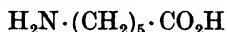
gives a 20–30 per cent. yield of the seven-membered lactam, the rest of the product being a polymeric amide of high molecular weight,

$$H_2N(CH_2)_5 \cdot CO[NH \cdot (CH_2)_5 \cdot CO]_n NH \cdot (CH_2)_5 \cdot CO_2H.$$
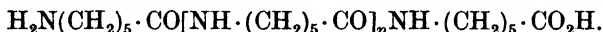
Finally, amino-acids with a greater number of carbon atoms separating the amine and carboxyl groups give nothing but the polymeric products. The dependence of the ring formation on the number of carbon atoms separating the amino and carboxyl groups is exactly the same as in the formation of lactones from hydroxy-acids. Lactams with large rings can be obtained by O. Wallach's method,[2] the Beckmann rearrangement of the oximes of cyclic ketones (see p. 472).

Amides of Dibasic Acids

Dibasic acids can form both monoamides and diamides. The former still contain a carboxyl group and are known as -amic acids, e.g. succinamic acid, $HO_2C \cdot CH_2 \cdot CH_2 \cdot CONH_2$. Oxamic acid, $HO_2C \cdot CONH_2$, is a crystalline solid (m.p. 210°, decomp.) sparingly soluble in water: it can be obtained by heating acid ammonium oxalate, $HO_2C \cdot CO_2NH_4$, or by the partial hydrolysis of its ethyl ester. This latter compound is commonly called oxamethane and is formed by the interaction of diethyl oxalate and ammonia in equimolecular proportions in alcohol. Succinamic acid,

[1] E. L. Hirst, *J.C.S.* 1933, 1273.   [2] *Annalen*, 1900, **312**, 171.

$HO_2C \cdot CH_2 \cdot CH_2 \cdot CONH_2$, on heating passes readily into the five-membered cyclic imide succinimide (see p. 152).

The monoamide of aminosuccinic acid (aspartic acid),

$$H_2N \cdot CO \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$$
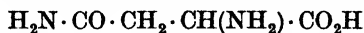
(asparagine), occurs in nature in d- and l-forms, more commonly the latter. The l-form is tasteless while the d-form is sweet; this difference is common to a number of similar compounds and is an indication, as L. Pasteur pointed out, that the nerve-endings of the tongue and palate must contain optically active substances. Asparagine and glutamine, the monoamide of α-aminoglutaric acid, $H_2N \cdot CO \cdot (CH_2)_2 \cdot CH(NH_2) \cdot CO_2H$, both occur in germinating seeds and as protein constituents: they are of great importance in protein metabolism.

The diamides of dibasic acids are a curious class of compounds. They can be obtained by the action of excess of ammonia on the esters or chlorides of the acids. The acid chloride of phthalic acid is an exception. With aqueous ammonia it gives o-cyanobenzoic acid, and this is one of the indications of the abnormal structure of phthalyl chloride.
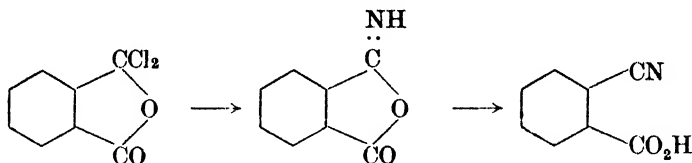
The dimethyl ester of phthalic acid reacts normally with ammonia. The diamides derived from acids such as succinic acid or phthalic acid lose ammonia readily on heating to give the cyclic imides
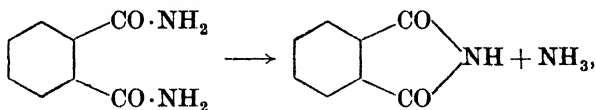
but the remainder do not and, as usually obtained, are amorphous powders, very sparingly soluble in all solvents, and with no true melting-points. They decompose on heating at temperatures of the order of 300–400° to a variety of products. They behave, in fact, as though they were compounds of very high molecular weight. These characteristics persist in the aliphatic series whatever the number of carbon atoms separating the two amide groups, and are also found in the diamides of aromatic acids such as terephthalic acid (benzene p-dicarboxylic acid). In nearly all homologous series of straight chain compounds with a reactive group at either end the melting-points of the higher members approach the temperature of 120° as the chain lengthens; this simple rule arises from the fact that when the chain is long the forces holding the molecules in the crystal lattice are those between the carbon chains, and these are the same for all the compounds.[1] The diamides are a marked exception to this rule, and retain their high melting-points and insolubility throughout the

[1] J. Timmermans, *Institut International de Chimie Solvay*, 1931, p. 202.

series. The same behaviour is shown by the dianilides and other amides in which one hydrogen atom of each amine group has been replaced by a hydro-carbon residue, but the N, N′-tetra-substituted compounds, such as $(CONMe_2)_2$, are more normal in their physical properties. The way in which a compound such as oxamide associates to a complex of high molecular weight is unknown.

Oxamide on heating with phosphorous pentoxide gives cyanogen:

$$(CONH_2)_2 \longrightarrow (CN)_2 + 2H_2O$$
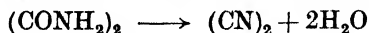
the reverse process can be achieved at room temperature in aqueous solution by addition of acetaldehyde, a curious catalytic action discovered by Liebig. W. Langenbeck[1] has shown that an intermediate compound is formed containing the aldehyde, cyanogen, and water which readily breaks down to the aldehyde and oxamide.

There are indications that two isomeric forms of the diamide of succinic acid exist. If the diethyl ester is treated with ammonia a diamide (m.p. 266°) showing the typical insolubility is formed. The action of ammonia on succinyl chloride, however, gives a hygroscopic substance of the same composition,[2] to which has been allotted the rather improbable structure

$$\begin{array}{l} CH_2\!\!-\!\!C(NH_2)_2 \\ \quad | \qquad \qquad >\!\!O \\ CH_2\!\!-\!\!CO \end{array}$$
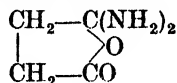
derived from the unsymmetrical form known to occur in certain of these acid chlorides. There are also two diamides of methyl-succinic acid,[3] but only one diamide of phthalic acid is known.

The half anilides of dibasic acids are known as -anilic acids, and are readily formed by the action of the anhydrides of dibasic acids with aniline. In the case of polymeric long-chain anhydrides of the type $HO_2C\cdot(CH_2)_x\cdot CO\cdot O\cdot CO\cdot(CH_2)_x\cdot CO\cdot O\cdot CO\cdot$, etc., which are formed by acids in which the number of carbon atoms between the carboxyl groups makes the formation of a cyclic anhydride unlikely, the product of the reaction with aniline consists of 1 part of the dianilide, 1 part of the acid, and 2 parts of the -anilic acid.[4] This is precisely the ratio that would be expected: at each anhydride linking in the chain the aniline molecule can react in one of two ways:

either
$$\begin{array}{c} -CO\cdot O\cdot\vdots CO- \\ \qquad \vdots \\ H\cdot\vdots NH\phi \end{array} \longrightarrow -CO_2\cdot H + \phi NH\cdot CO-$$

or
$$\begin{array}{c} -CO\cdot\vdots O\cdot CO- \\ \qquad \vdots \\ \phi NH\cdot\vdots H \end{array} \longrightarrow -CO\cdot NH\phi + HO_2C-$$
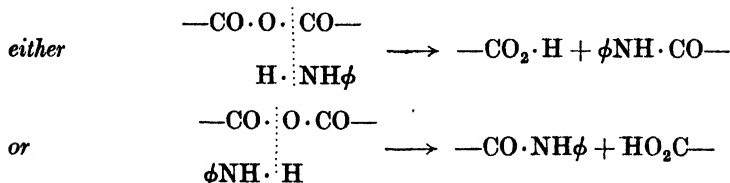
and if the chance of either event is the same, the proportion in which the products are formed will be that found experimentally.

[1] *Annalen*, 1929, **469**, 16.　　　　[2] V. Auger, *Ann. Chim. Phys.* 1891, (vi), **22**, 326.
[3] G. F. Morrell, *J.C.S.* 1914, **105**, 1733.
[4] W. H. Carothers, *J. Amer. C. S.* 1930, **52**, 3470.

Thioamides and Thioanilides.

In these compounds sulphur takes the place of oxygen. They can be obtained by the action of phosphorus pentasulphide on amides, or better by that of aluminium sulphide in the presence of hydrated sodium sulphate on the amide or the ammonium salt of the acid.[1] They are also formed by the action of hydrogen sulphide on nitriles:

$$CH_3 \cdot C \colon N + H_2S \longrightarrow CH_3 \cdot CS \cdot NH_2.$$
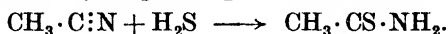
They are very easily hydrolysed to the acid, ammonia, and hydrogen sulphide. They are useful for the preparation of compounds such as amidines and amidoximes,

$$CH_3 \cdot CS \cdot NH_2 + NH_3 \longrightarrow CH_3 \cdot C(\colon NH) \cdot NH_2$$
$$CH_3 \cdot CS \cdot NH_2 + H_2NOH \longrightarrow CH_3 \cdot C(\colon NOH) \cdot NH_2.$$
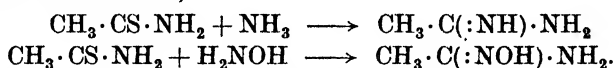
They frequently react as though they possessed the isothioamide structure, $R \cdot C \underset{NH}{\overset{SH}{\diagdown}}$: thus with alkyl halides they give S-ethers, $R \cdot C \underset{NH}{\overset{SR'}{\diagdown}}$, and with chloracetone thiazoles.

$$R \cdot C \underset{NH}{\overset{SH}{\diagdown}} + \underset{ClCH}{\overset{HO \cdot C \cdot CH_3}{\|}} \longrightarrow R \cdot C \underset{N-CH}{\overset{S-C \cdot CH_3}{\diagdown}}$$
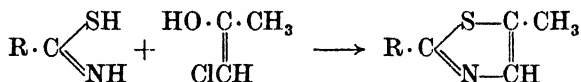
Their actual constitution under various conditions is, however, as uncertain as that of the amides themselves. Thioformamide, which R. Willstätter and T. Wirth obtained[2] by the action of phosphorus pentasulphide on formamide, shows an acid reaction in solution, which suggests the imine structure $H \cdot C \underset{NH}{\overset{SH}{\diagdown}}$, but Hantzsch compared the absorption spectrum in the ultra-violet of thioacetamide with that of its S-methyl derivative, $CH_3 \cdot C \underset{NH}{\overset{SMe}{\diagdown}}$, in which the iso structure is fixed, and that of its piperidyl derivative, $CH_3 \cdot CS \cdot NC_5H_{10}$, which must have the amide structure. He found that in ether, chloroform, and water the unsubstituted thioamide resembled the piperidyl derivative, a fact which seems to indicate the true amide structure for thioacetamide.

Since formamide decomposes into ammonia and carbon monoxide on boiling, it is possible that thioformamide might give the unknown carbon monosulphide, CS. In fact it decomposes by the other route into hydrogen sulphide and prussic acid.

The thioanilides are more markedly acidic than the anilides, and dissolve in aqueous alkalis from which they are reprecipitated by carbon dioxide. The salts probably have the imino structure $R \cdot C \underset{N\phi}{\overset{S^-}{\diagdown}}$ [Na].

They are oxidized by potassium ferricyanide to benzthiazoles:
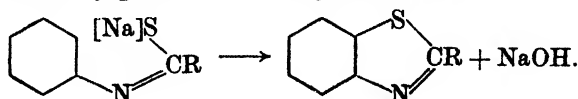
[1] K. Kindler and F. Finndorf, *Ber.* 1921, **54**, 1079. [2] *Ber.* 1909, **42**, 1908.

Imides

The imide , are the cyclic secondary amides of the dibasic acids:

$$(CH_2)_n \diagup^{CO_2H}_{\diagdown CO_2H} + NH_3 \longrightarrow (CH_2)_n \diagup^{CO}_{\diagdown CO} \diagup NH + 2H_2O.$$
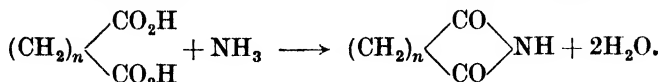
As would be expected they are formed with ease in the cases where the ring contains five or six members. Oxalimide is unknown, but its phenyl derivative, oxanil $\diagup^{CO}_{\diagdown CO} N\phi$, is said to be formed by the action of thionyl chloride on oxanilic acid.[1] The compound has no melting-point and is soluble only in hot nitrobenzene, facts which suggest that it is a polymer of high molecular weight, but ebullioscopic determination of the molecular weight in nitrobenzene indicates that it is monomolecular. Attempts to prepare the unsubstituted imide of oxalic acid result in the formation of tetraketopiperazine $NH \diagup^{CO—CO}_{\diagdown CO—CO} \diagup NH$.[2]

Malonic imide is unknown, although again it is stated that the corresponding anil can be obtained, but succinimide and glutarimide are well-known compounds, obtained by heating the ammonium salt, monoamides or diamides of the acids, or very conveniently by heating the anhydrides in a stream of ammonia or with urea. Succinimide can be reduced to pyrrole by heating it with zinc dust, to pyrrolidine with sodium and alcohol, and to pyrrolidone by the electrolytic method.

$$CH{=}CH \diagup^{}_{\diagdown} \underset{CH{=}CH}{|} \diagup NH \quad \text{pyrrole}$$

$$CH_2{\cdot}CO \diagup^{}_{\diagdown} \underset{CH_2{\cdot}CO}{|} \diagup NH \longrightarrow CH_2{—}CH_2 \diagup^{}_{\diagdown} \underset{CH_2{—}CH_2}{|} \diagup NH \quad \text{pyrrolidine}$$

$$CH_2{—}CO \diagup^{}_{\diagdown} \underset{CH_2{—}CH_2}{|} \diagup NH \quad \text{pyrrolidone}$$
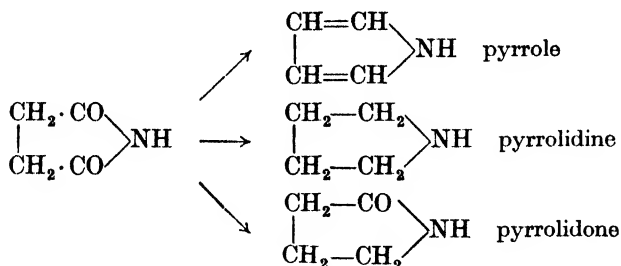
Glutarimide similarly gives a small yield of pyridine on distillation with zinc dust.

The most important aromatic imide is that of phthalic acid, which has been used as an intermediate in an indigo synthesis (see p. 509), and is a valuable reagent in Gabriel's preparation of primary amines (see p. 14). It can be obtained from phthalic anhydride by heating with urea or in a stream of dry ammonia. Isophthalic acid (benzene 1,3-dicarboxylic acid) forms no imide; the rigid structure of the benzene ring holds the carboxyl groups too far apart for ring closure, in spite of the fact that the ring would contain six members. Homophthalic acid, however, gives an imide

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[1] W. H. Warren and R. A. Briggs, *Ber.* 1931, **64**, 26.
[2] A. T. de Moulpied and A. Rule, *J.C.S.* 1907, **91**, 176.

which on treatment with phosphoryl chloride followed by reduction is converted into isoquinoline.

Homophthalic acid.
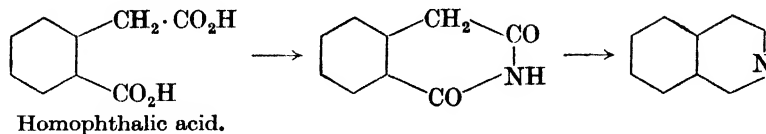
The imides are weak acids and give rise to a series of salts with metals. Succinimide forms a potassium salt with alcoholic potash, and phthalimide is sufficiently acid to dissolve in aqueous potash. With alkyl halides the salts give substituted imides in which the alkyl group is attached to the nitrogen atom, as is shown by the products of their hydrolysis (see p. 14).

Amido-chlorides, Imino-chlorides, and Imino-ethers

The action of phosphorus pentachloride on a simple amide leads to the nitrile, but intermediate compounds can be isolated which have been called amido-chlorides and imino-chlorides and to which the formulae $R \cdot CCl_2 \cdot NH_2$ and $R \cdot CCl:NH$ have been allotted. Whether these structures are correct seems doubtful. Many of the reactions of the compounds suggest that they are complexes of the nitrile with hydrogen chloride, possibly of the nature of salts.[1] They lose hydrogen chloride very readily and with water give the nitrile $R \cdot CN$ at once. The imino-chloride does not react with ammonia to give the amidine $R \cdot C(NH_2):NH$, but only the nitrile. On the other hand, the Hoesch-Gattermann synthesis of aromatic hydroxy aldehydes and ketones, which is discussed later (p. 314), suggests that the imino-chlorides exist, at least in solution.

Some mono-N-substituted amides, however, form definite imino-chlorides with phosphorus pentachloride, to which the formula $R \cdot CCl:NR'$ must be allotted. Such are the substituted benzamides and the alkyl amides and anilides of aliphatic acids of the type $R_3C \cdot CO \cdot NHR'$. Benz-phenylimino-chloride, $\phi \cdot CCl:N\phi$, obtained from benzanilide, is a stable compound boiling undecomposed at 310° and hydrolysed by water to benzanilide. If, however, the acid contains one or two hydrogen atoms attached to the α-carbon atom, as in isobutyric anilide, $Me_2CH \cdot CONH\phi$, or propionic anilide, $MeCH_2 \cdot CONH\phi$, the imino-chloride is much more unstable[2] and in many cases cannot be obtained. Two molecules condense together readily to form an amidine derivative: e.g., from acetanilide, the compound $CH_3 \cdot C(:N\phi) \cdot N\phi \cdot CCl:CH_2$. An interesting case where the imino-chlorides are stable is when a substituent is present in the ortho position to the amino group in the benzene ring: the condensation to the amidine seems to be prevented by steric hindrance, and thus the imino-chloride can be obtained and often distilled.[3]

[1] A. Hantzsch, *Ber.* 1931, **64**, 667.
[2] J. von Braun, F. Jostes, and W. Münch, *Annalen*, 1927, **453**, 113.
[3] J. von Braun and H. Silbermann, *Ber.* 1930, **63**, 498.

If excess of phosphorus pentachloride (3 molecular proportions) is allowed to react with an amide of the type $R \cdot CH_2 \cdot CO \cdot NHR'$, where R and R' are either aromatic or aliphatic residues, the product is the imino-chloride of the dichloro acid, $R \cdot CCl_2 \cdot CCl : NR'$, and similarly $R_2CH \cdot CO \cdot NHR'$ gives the imino-chloride $R_2CCl \cdot CCl : NR'$. These imino-chlorides are stable compounds and can be hydrolysed to the corresponding acids, so that the method can be used for obtaining the chlorinated acids.[1]

The imino-ethers, which can also be regarded as esters of imino-acids and are sometimes called imino-esters, have the general formula $R \cdot C(OR') : NH$, or, if derived from mono-substituted amides, $R \cdot C(OR') : NR''$. Our knowledge of the group is largely due to A. Pinner. They are formed by the action of alkyl halides on the metallic salts of the amides, but are most easily obtained by passing dry hydrogen chloride into an equi-molecular mixture of a nitrile and an alcohol in a well-cooled ether solution, when the hydrochloride of the imino-ether crystallizes:

$$R \cdot C \vdots N + EtOH + HCl \longrightarrow R \cdot C(OEt) : NH, HCl.$$
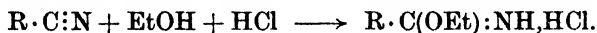
These hydrochlorides lose alkyl chloride on heating and form the amide:

$$R \cdot C(OEt) : NH, HCl \longrightarrow R \cdot CO \cdot NH_2 + EtCl.$$
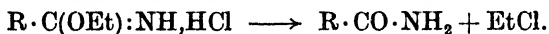
On treatment with excess of the alcohol they form the ortho ester of the original acid:[2]

$$R \cdot C(OEt) : NH, HCl + 2EtOH \longrightarrow R \cdot C(OEt)_3 + NH_4Cl.$$

If neutralized with sodium carbonate under ether, the hydrochloride can be converted into the free imino-ether. Acetimino-ethyl-ether, $CH_3 \cdot C(OEt) : NH$, is a liquid with a characteristic smell boiling at 94°. The simple ethers, with no substituent on the nitrogen atom, break up on heating into nitrile and alcohol. On the other hand, the N-substituted compounds undergo an interesting rearrangement. They are prepared by alkylation of the simple ethers, or by converting the N-substituted amide into the imino-chloride and allowing this to react with sodium alkoxide:

$$R \cdot CO \cdot NH\phi \longrightarrow R \cdot CCl : N\phi \longrightarrow R \cdot C(OEt) : N\phi.$$
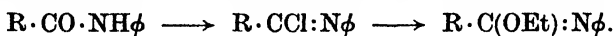
If heated to 200–300°, the compounds rearrange to di-substituted amides.

$$CH_3 - C \underset{N\phi}{\overset{OEt}{\big\langle}} \longrightarrow CH_3 - C \underset{NEt\phi}{\overset{O}{\big\langle}}$$
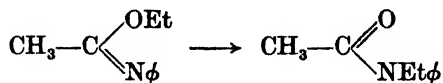
This isomeric change recalls the tautomerism between an amide and an isoamide, but is not reversible. The kinetics and mechanism of the change have been studied in detail by A. W. Chapman[3] in the case of the aromatic

[1] J. von Braun and A. Heymons, *Ber.* 1930, **63**, 502.
[2] H. Reitter and E. Hess, *Ber.* 1907, **40**, 3020.
[3] *J.C.S.* 1925, **127**, 1992; 1927, 1743.

derivatives, and he has shown conclusively that it is entirely an intra-molecular process. He found that the change of N-phenylbenziminophenyl ether into benzoyl diphenylamine,

$$\phi \cdot C(O\phi) : N\phi \longrightarrow \phi \cdot CO \cdot N\phi_2,$$
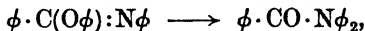
is a unimolecular reaction, which gives no by-products and can be followed by freezing-point determinations of the mixture. When a mixture of the phenyl compound and the corresponding p-tolyl compound undergoes re-arrangement, the product consists solely of benzoyl diphenylamine and p-toluylditolylamine. There is no product containing both phenyl and tolyl groups, such as would be expected if the migratory group actually split off from the molecule and existed for any time as a free radical or an ion during the rearrangement, or if the latter were a bimolecular pro-cess. The two rearrangements proceed in the mixture completely independently, and thus must be intramolecular. In the case of the corresponding thio-ethers, $\phi \cdot C(S\phi) : N\phi$, there are indications that at a temperature of 320° the change of imino-ether into amide is reversible.[1]

The conversion of an imino-ether, especially of the aliphatic ethers, into di-substituted amides is brought about at a much lower temperature by the addition of an alkyl halide. The mechanism of this reaction is most probably the formation of a quaternary salt followed by the loss of alkyl halide:

$$R \cdot C(OEt) : N\phi + EtI \longrightarrow R \cdot C(OEt) : N\phi Et[I] \longrightarrow R \cdot CO \cdot N\phi Et + EtI.$$
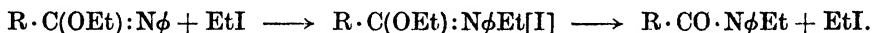
This is indicated by the fact that if the halide of a different alkyl radical is used, there is often an exchange of alkyl groups:[2]

$$R \cdot C(OEt) : N\phi + MeI \longrightarrow R \cdot CO \cdot N\phi Me + EtI.$$
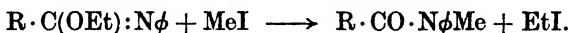
AMIDINES

With ammonia, the imino-ethers react like esters, giving amidines:

$$R \cdot C(OEt) : NH + NH_3 \longrightarrow R \cdot C(NH_2) : NH + EtOH.$$
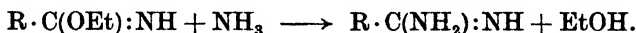
Amidines can also be obtained by heating the amides in a stream of hydro-gen chloride, or the nitriles with ammonium chloride:

$$2CH_3 \cdot CONH_2 + HCl \longrightarrow CH_3 \cdot CO_2H + CH_3 \cdot C(NH_2) : NH, HCl$$

$$CH_3 \cdot CN + NH_4Cl \longrightarrow CH_3 \cdot C(NH_2) : NH, HCl.$$
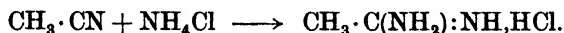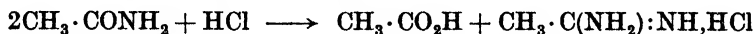
The amidines are easily hydrolysed to the acid and ammonia. They are strong monacid bases, with a marked alkaline reaction in solution, and form stable salts with acids. The amidine kation has the constitution $-C\!\!\left\langle\begin{smallmatrix} NH_2 \\ NH_2^+ \end{smallmatrix}\right.$. The distinction between the two nitrogen atoms which this formula implies has no real existence; either nitrogen atom could be written as doubly bound to the carbon atom and carrying a positive

[1] A. W. Chapman, *J.C.S.* 1926, 2296.   [2] G. D. Lander, *J.C.S.* 1903, **83**, 406.

charge. The actual state of the kation is that of a resonance-hybrid of the two alternatives, and in this respect the amidine kation is analogous to the nitro group and the carboxylate anion, in neither of which is there any distinction between the oxygen atoms.

$$-N\diagdown^{O}_{O} \qquad -C\diagdown^{O}_{O^-}$$

Amidines condense with β-ketonic esters and β-diketones to form derivatives of pyrimidine:

$$R\cdot C\diagup^{NH}_{NH_2} + \genfrac{}{}{0pt}{}{OC\cdot CH_3}{OC\cdot OEt}\!\!>\!CH_2 \longrightarrow R\cdot C\diagup^{N-C\cdot CH_3}_{N=C\cdot OEt}\!\!>\!CH$$

and with α-bromoketones or α-ketonic alcohols to glyoxalines:

$$R\cdot C\diagup^{NH}_{NH_2} + \genfrac{}{}{0pt}{}{OC\cdot\phi}{BrCH_2} \longrightarrow R\cdot C\diagup^{N-C\cdot\phi}_{NH-CH}$$
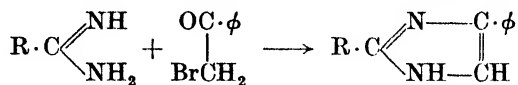
N-substituted amidines can be readily obtained by boiling a primary or secondary amine with a substituted amide in solution in phosphorus trichloride:[1]

$$R\cdot C\diagdown^{O}_{NHR'} + H_2NR'' \searrow \atop R\cdot C\diagdown^{O}_{NHR''} + H_2NR' \nearrow \left\{ \begin{array}{c} R\cdot C\diagup^{NR''}_{NHR'} \\ or \\ R\cdot C\diagup^{NR'}_{NHR''} \end{array} \right.$$
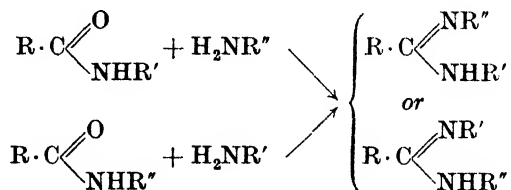
The same product is obtained if the N-substituents in the two reactants are reversed. The amidine can have either of two formulae, and in its reactions behaves like a tautomeric mixture of the two.

If all the hydrogen atoms are replaced by hydrocarbon radicals, the two compounds $R\cdot C(NAB){:}NA$ and $R\cdot C(NA_2){:}NB$ are distinct. When they are heated rearrangement takes place and an equilibrium is set up between the two compounds. This change has been investigated in detail by A. W. Chapman[2] who has shown that, as in the case of the imino-ethers, the arrangement is intra-molecular.

Confusion existed at one time over substances which were thought to be the true isoamides with the structure $R\cdot C(OH){:}NH$, which could be obtained from certain α-hydroxy acids, by the action of ammonia on the anhydride. They were shown by Hantzsch to have a molecular weight twice as large as that required by the above formula, and H. G. Rule[3] has proved that they are salts of amidines of the general formula

$$R\cdot C(NH_2){:}NH, \; R\cdot CO_2H.$$

[1] See M. Sen and J. N. Rây, *J.C.S.* 1926, 646.
[2] *J.C.S.* 1929, 2133; 1930, 2462; 1932, 1771.   [3] *J.C.S.* 1918, **113**, 3.

THE AMIDES OF THE SULPHONIC ACIDS

The amides of the aliphatic sulphonic acids have been very little investigated. In the aromatic series, however, the sulphonic acids are readily obtained by direct sulphonation, and their amides, which are usually referred to as sulphonamides, present several points of interest.

The simple amides containing the group —$SO_2 \cdot NH_2$ are almost invariably prepared by the action of ammonia on the sulphonic chloride:

$$R \cdot SO_2 \cdot Cl + NH_3 \longrightarrow R \cdot SO_2 \cdot NH_2 + HCl.$$
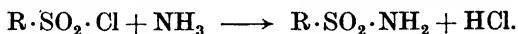
Sometimes the chloride is gently warmed with excess of solid ammonium carbonate; sometimes better yields are obtained if it is treated with concentrated aqueous ammonia or if gaseous ammonia is passed through its solution in an inert solvent. The mono- and di-N-substituted sulphonamides can be obtained in a similar way from the primary and secondary amines. In these cases it is often of advantage to use pyridine as solvent; the reaction then proceeds more readily and at a lower temperature. It must be noted that the sulphonamides cannot be prepared by the action of ammonia upon the sulphonic esters; the reaction leads to the formation of a primary amine, and the ammonium salt of the sulphonic acid. This behaviour is similar to that of the esters of nitric and sulphuric acids (p. 14), but unlike that of the carboxylic esters (p. 137).

The unsubstituted sulphonamides usually crystallize very well from hot water or alcohol; they are the simplest crystalline derivatives of a sulphonic acid that can be easily prepared and purified and are often used for the characterization and identification of sulphonic acids. Sulphonamides and sulphonanilides can be hydrolysed to their component acid and amine by concentrated sulphuric acid in the cold,[1] but they are much more resistant to hydrolysis than the amides of carboxylic acids. The latter are rapidly hydrolysed by aqueous alkalis; sulphonamides, on the other hand, undergo no hydrolysis, but dissolve with the formation of salts. The sulphonamides are not strong acids; their sodium and potassium salts show a strong alkaline reaction in aqueous solutions, and even in the presence of excess alkali ether will extract some of the amide from the solution.[2] In liquid ammonia, however, the sulphonamides give conducting solutions and behave as fairly strong acids.[3] This salt formation with caustic alkalis is common to all sulphonamides in which there is at least one hydrogen atom attached to nitrogen: it is shown by the mono-substituted sulphonamides of the type $R \cdot SO_2 \cdot NHR'$ and by the N-chlor compounds $R \cdot SO_2 \cdot NHCl$ which are discussed below. The di-substituted amides of the type $R \cdot SO_2 \cdot NR_2'$ are not alkali-soluble, and upon this distinction is based Hinsberg's method of separation of primary and secondary amines (see p. 19).

The structure of the anion of these alkali salts of the sulphonamides has

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[1] G. Schroeter and O. Eisleb, *Annalen*, 1909, **367**, 157.

[2] W. Marckwald and A. von Droste-Huelshoff, *Ber.* 1898, **31**, 3262, footnote.

[3] E. C. Franklin and C. A. Kraus, *Amer. Chem. J.* 1909, **23**, 292.

been a matter of some uncertainty. Hantzsch[1] suggested that the salts might be derived from the isoamide structure, $R \cdot SO(OH):NH$, which is analogous to the isoamide structure for the carboxylic amides discussed above. Such a structure would give rise to an anion (I) which might appear to differ from the anion (II) derived from the true amide. Neither of these formulae, however, is a satisfactory picture of the mode of linking of the atoms in the anion. There are many indications that in the sulphonic

$$\text{I. } R \cdot S \underset{\diagdown NH}{\overset{\diagup O}{<}} O^- \qquad \text{II. } R \cdot S \underset{\diagdown NH^-}{\overset{\diagup O}{<}} O \qquad \text{III. } R \cdot S \underset{\diagdown NH_2}{\overset{\diagup O}{\rightarrow}} O$$
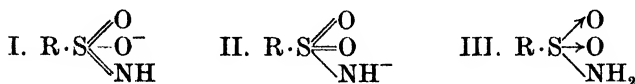
acid two oxygen atoms are attached to the sulphur by co-ordinate (semipolar) links; its amide can thus be written as (III). When this molecule loses a hydrogen atom and becomes an anion, it may have the structure (IV), but this will be identical with the structure (V). This point becomes immediately apparent if structures (IV) and (V) are written, not with the conventional signs for the valencies, but with dots representing the electrons involved in valency formation. Both formulae then reduce to the one formula (VI).

$$\text{IV. } R \cdot S \underset{\diagdown NH^-}{\overset{\diagup O}{\rightarrow}} O \qquad \text{V. } R \cdot S \underset{\diagdown NH}{\overset{\diagup O}{<}} O^- \qquad \text{VI. } \begin{matrix} :O: \\ R:S:O: \\ :N: \\ H \end{matrix}$$
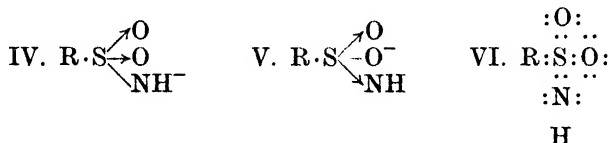
Alkyl derivatives corresponding to the isoamide structure are unknown: alkylation of a sulphonamide under any conditions leads to an N-alkyl compound, identical with that obtained by the action of the sulphonic chloride on the corresponding alkylamine.[2] The simple unsubstituted sulphonamides condense with formaldehyde to give resins which can be used as a plastic material.[3]

When toluene is sulphonated, the product consists almost entirely of the ortho- and para-sulphonic acids; at temperatures below 100° the ortho compound is 40–50 per cent. of the whole. The amides derived from both of these acids lead to compounds of practical importance.

In 1879 I. Remsen and C. Fahlberg investigated the oxidation of o-toluene sulphonamide; they obtained different products according to the conditions of oxidation. Fahlberg went back from the laboratory one day to his evening meal and noticed that the bread he ate tasted extremely sweet. He traced the taste to his hands and then returned to the laboratory and found that one of the oxidation products was the cause. In this way saccharin was discovered. If the sulphonamide is oxidized by alkaline permanganate, the methyl group becomes a carboxyl group and the salt of o-carboxybenzene sulphonamide (VII) is formed. If the solution is kept neutral during the oxidation or if electrolytic oxidation is used, the pro-

[1] *Ber.* 1901, **34**, 3148.　　　　[2] A. Hantzsch, loc. cit.　　　　[3] Eng. Pat. 342614.

duct is saccharin (VIII), the cyclic imide of o-carboxybenzene sulphonic acid. It is also formed by heating the free carboxysulphonamide.
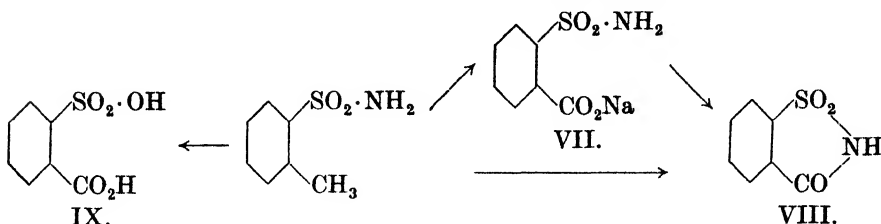
Oxidation with permanganate in acid solution brings about hydrolysis of the amide grouping and o-carboxybenzene sulphonic acid (IX) results.

Saccharin is a white crystalline solid melting at 227°: it sublimes with great ease and is sparingly soluble in water. It is estimated to be 300 times as sweet as cane sugar, and is used as a sweetening agent and as a sugar substitute where the use of sugar is undesirable. It has its own physiological effects which are not negligible. It is a fairly strong acid and dissolves readily in aqueous alkali carbonates to give the alkali salts. It is thus a stronger acid than phthalimide, as would be expected since the sulphonic acids are much stronger than the carboxylic. The sodium and ammonium salts are freely soluble in water; the latter is often used as a sweetening agent and is said to be more than twice as sweet as saccharin itself.

The amide of p-toluene sulphonic acid gives rise to chloramine-T, a valuable antiseptic in the treatment of wounds. F. D. Chattaway[1] first prepared compounds of the type; he found that if an unsubstituted sulphonamide is dissolved in excess of a solution of bleaching-powder and acetic acid added with cooling, the sulphodichloramide, $R \cdot SO_2 \cdot NCl_2$, separates as an oil which rapidly solidifies. This is a typical preparation of an N-chlor compound by the use of hypochlorous acid:

$$:NH + HOCl \longrightarrow :NCl + H_2O.$$
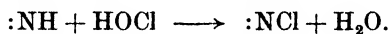
These compounds have the usual properties of substances in which chlorine is attached to nitrogen; they react with dilute hydrochloric acid with liberation of chlorine, and liberate iodine from acidified potassium iodide and sulphur from hydrogen sulphide.

$$R \cdot SO_2 \cdot NCl_2 + 2HCl \longrightarrow R \cdot SO_2 \cdot NH_2 + 2Cl_2$$

They are, however, very much more stable than the majority of N-chlor compounds and many of them melt without decomposition. If such a sulphodichloramide is treated with warm aqueous caustic soda, on cooling crystals of the sodium salt of the sulphomonochloramide are deposited:

$$R \cdot SO_2 \cdot NCl_2 + 2NaOH \longrightarrow R \cdot SO_2 \cdot NCl\,[Na] + NaOCl + H_2O.$$
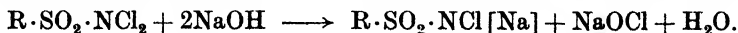
The same salt can be obtained directly from the sulphonamide by the action of sodium hypochlorite and caustic soda. Of salts of this kind the

[1] *J.C.S.* 1905, 87, 145.

one that is best known is that derived from p-toluene sulphonic acid, because this latter compound is a by-product in saccharin manufacture and is thus cheap and available in quantity. This compound, the sodium salt of p-toluene sulphochloramide, is known as chloramine-T. Its solutions are powerfully germicidal, like those of almost all N-chlor compounds, but have the advantage of greater stability and have been widely used in dressings for wounds.[1] It is of interest to note that the aliphatic sulphonamides such as

$$CH_3 \cdot SO_2 \cdot NH_2, \quad CH_2 : CH \cdot SO_2 \cdot NH_2, \quad \text{and} \quad \phi \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot SO_2 \cdot NH_2$$

do not react with sodium hypochlorite; on the other hand, all aromatic sulphonamides react readily, as does also toluene-ω-sulphonamide, $\phi \cdot CH_2 \cdot SO_2 \cdot NH_2$.[2]

The use during the Great War of chloramine-T as an antiseptic and of $\beta\beta'$-dichlordiethyl sulphide, $(Cl \cdot CH_2 \cdot CH_2)S$, in gas warfare led to the discovery that the two compounds will condense together with elimination of sodium chloride to give a crystalline compound.[3] The reaction is a general one and takes place between the salt of any sulphochloramide and any thio-ether; the product is described as a sulphilimine and is hydrolysed by boiling water or dilute acids, with the production of the original sulphonamide. These compounds were originally formulated by Mann and Pope as containing tetracovalent sulphur:

$$R \cdot SO_2 \cdot NCl[Na] + R_2'S \longrightarrow R \cdot SO_2 \cdot N : SR_2' + NaCl.$$
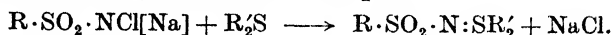
This state of combination is, however, very unlikely for the sulphur atom; the so-called tetravalent sulphur compounds are either of the type of the sulphonium salts $[R_3S]Br$ or of the sulphoxides, $R_2S \rightarrow O$, in both of which classes the sulphur atom is tricovalent. Hence a more probable constitution is one analogous to the sulphoxides in which nitrogen and sulphur are united by a co-ordinate link, i.e. $R \cdot SO_2 \cdot N \leftarrow SR_2$. If this is so, and a thio-ether containing two different radicals is used, the sulphilimine should contain a sulphur atom which from the point of view of stereochemistry is similar to that in a sulphinic ester, $\begin{smallmatrix} R \\ EtO \end{smallmatrix} \!\! > \!\! S \rightarrow O$, and it should be possible to resolve such a sulphilimine into optical antimers. This was achieved by S. G. Clarke, J. Kenyon, and H. Phillips,[4] who were the first to propose this constitution, in the case of m-carboxyphenylmethylsulphine-p-toluene-sulphonylimine (X); the active compound shows great optical stability. The corresponding ethyl compound has also been resolved.[5]

$$\text{X. } Me \cdot C_6H_4 \cdot SO_2 \cdot N \longleftarrow SMe \cdot C_6H_4 \cdot CO_2H.$$
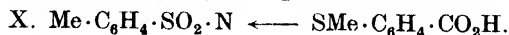
Derivatives of p-amino-benzene-sulphonamide (sulphanilamide),

$$RNH \cdot C_6H_4 \cdot SO_2 \cdot NH_2,$$
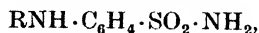
are of outstanding importance as chemotherapeutic agents. A comprehensive article has been given by E. H. Northey.[6]

[1] H. D. Dakin, J. B. Cohen, M. Daufresne, and J. Kenyon, *Proc. Roy. Soc.* B, 1916, **89**, 232.   [2] P. W. Clutterbuck and J. B. Cohen, *J.C.S.* 1923, **123**, 2507.
[3] F. G. Mann and W. J. Pope, ibid. 1922, **121**, 1052.   [4] Ibid. 1927, 188.
[5] J. Holloway, J. Kenyon, and H. Phillips, ibid. 1928, 3000.
[6] *Chem. Rev.* 1940, **27**, 85–197.

CHAPTER VI

HYDROXYLAMINE DERIVATIVES

THE organic derivatives of hydroxylamine, NH_2OH, may be divided into four classes:

1. The alkyl and aryl substitution products in which one or more hydrogen atoms are replaced by as many organic radicals.

2. The amine oxides derived from the tautomeric form of hydroxylamine, $H_3N{\rightarrow}O$.

3. The oximes, possessing the general formula $\begin{matrix} R \\ R' \end{matrix}{>}C{:}NOH$, in which two hydrogen atoms are replaced by a divalent radical.

4. The acyl substitution products, the so-called hydroxamic acids, and their derivatives.

THE ALKYL- AND ARYL-HYDROXYLAMINES

Since hydroxylamine has the formula NH_2OH and an organic radical can replace a hydrogen atom attached either to nitrogen or oxygen, there are two series of monoalkyl and aryl derivatives, which have the general formulae NH_2OR and $NHR{\cdot}OH$. The former class are often referred to as α-, and the latter as β-hydroxylamines. It is less ambiguous, and therefore preferable, to call the two series the O- and the N-compounds.

The O-alkyl-hydroxylamines, such as the O-methyl compound NH_2OMe, are best obtained by the hydrolysis of the O-ethers formed in the alkylation of an oxime (see p. 173),[1] or by the hydrolysis of the O-ether of hydroxyurethane, which can be prepared from hydroxylamine and chloroformic ester.[2]

$$R_2C{:}NOH \longrightarrow R_2C{:}NOMe \xrightarrow{\text{HCl aq}} R_2CO + H_2NOMe$$

$$EtO{\cdot}CO{\cdot}Cl + NH_2OH \longrightarrow EtO{\cdot}CO{\cdot}NHOH \longrightarrow EtO{\cdot}CO{\cdot}NHOMe$$

$$\xrightarrow{\text{KOH}} EtOH + CO_2 + NH_2OMe$$
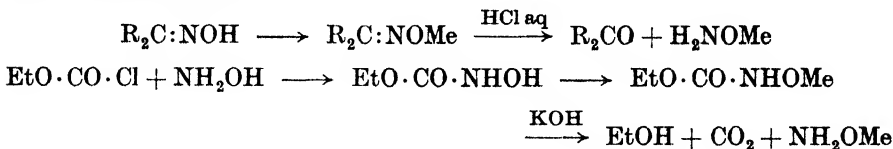
They are liquids soluble in water and volatile (NH_2OMe, b.p. 50°; NH_2OEt, b.p. 75°), and they behave as monacidic bases. Their constitution is shown by the fact that the ethyl compound is hydrolysed by hydrochloric acid at 150° to ethyl chloride and hydroxylamine, while the isomeric N-alkyl-hydroxylamines give products in which the alkyl group is attached to nitrogen.

The N-alkyl-hydroxylamines are low-melting volatile solids; they are soluble in water and are monacidic bases. N-methylhydroxylamine can

[1] J. Petraczek, *Ber.* 1883, **16**, 827.   [2] L. W. Jones, *Amer. Chem. J.* 1898, **20**, 39.

be obtained by a method similar to that used by Bamberger for the aryl compounds, namely, reduction of nitromethane by zinc dust in the presence of ammonium chloride; it is also formed by the hydrolysis of the N-methyl ethers of the oximes (see p. 173). N-Methylhydroxylamine is reduced by hydriodic acid to methylamine, which indicates its constitution, and it condenses with aldehydes to give the N-methyl ether of the oxime, $RCH:NMe \rightarrow O$. The O,N-dialkyl-hydroxylamines, such as $MeNH \cdot OMe$, can be obtained by the further alkylation of the O-ether of hydroxyurethane, followed by hydrolysis.[1] These compounds, like the mono-substituted ones, are easily oxidized and reduce Fehling's solution.

The fully methylated hydroxylamine, $Me_2N \cdot OMe$, which is a liquid boiling at 30°, has been prepared by the action of methyl iodide on O,N-dimethyl-hydroxylamine in ether;[2] it is not a reducing agent. It forms a quaternary methiodide with methyl iodide, which must have the constitution $[Me_3N \cdot OMe]I$. This is identical with the methiodide of trimethylamine oxide, a fact which is of importance for determining the structure of the salts of the amine oxides (see p. 168). Methyl groups attached to oxygen are usually much more readily removed by hydrolysis than methyl groups attached to nitrogen. Hence tri-substituted hydroxylamines on heating with acids are in part hydrolysed to the N,N-disubstituted compounds, which may undergo further transformations. If, however, they are of the type $R_2N \cdot OCH_2R'$, they show a tendency on such treatment to lose the aldehyde $R'CHO$, leaving the secondary amine R_2NH.[3]

N-phenylhydroxylamine has been investigated in great detail. It is an unstable compound, capable of undergoing a remarkable number of changes, and for some years all attempts to prepare it failed; during its preparation the reaction mixture must be kept neutral, since both in acid and alkaline solution it is transformed into other substances. It is usually prepared by Bamberger's method, the reduction of nitrobenzene by zinc dust and water in the presence of ammonium chloride,[4] and forms colourless needles melting at 82°. It can also be prepared by reduction of nitrobenzene with the calculated amount of hydrogen in the presence of palladized animal charcoal at room temperature,[5] and by the action of anhydrous hydrogen peroxide on $\phi NH \cdot MgBr$, obtained from aniline and phenyl magnesium bromide, in ether at —25°.[6] It is the first product of the oxidation of aniline by Caro's (permonosulphuric) acid in ether at low temperatures (see p. 53).

Phenylhydroxylamine is very readily oxidized and reduces Fehling's

[1] R. T. Major and E. E. Fleck, *J. Amer. C. S.* 1928, **50**, 480.

[2] L. W. Jones and R. T. Major, ibid. 2742.

[3] R. Behrend and K. Leuchs, *Annalen*, 1890, **257**, 203; J. Meisenheimer, *Ber.* 1919, **52**, 1667; T. D. Stewart and S. Maeser, *J. Amer. C. S.* 1924, **46**, 2583.

[4] *Organic Syntheses*, Collective vol. 1, p. 435.

[5] K. Brand and J. Steiner, *Ber.* 1922, **55**, 875.

[6] J. F. Durand and R. Naves, *C.r.* 1925, **180**, 521; B. Oddo and R. Binaghi, *Gazz.* 1924, **54**, 197.

solution and ammoniacal silver nitrate in the cold. The primary oxidation product is nitrosobenzene, which can be obtained in good yield if the right amount of chromic acid, potassium permanganate, or ferric chloride is used. It is also oxidized by the oxygen of the air and hence its solutions decompose on standing in open vessels. If the solution is neutral, the main product is azoxybenzene, formed by the condensation of nitrosobenzene with unchanged phenylhydroxylamine; at the same time hydrogen peroxide is formed, as in many oxidations by gaseous oxygen.

$$\phi \cdot NO + HO \cdot NH \cdot \phi \longrightarrow \phi \cdot NO : N \cdot \phi + H_2O$$

In alkaline solution atmospheric oxidation gives mainly azoxybenzene and nitrobenzene, but no hydrogen peroxide; the latter is presumably used up in the oxidation which leads to the nitro compound.

In the absence of air phenylhydroxylamine is converted on standing into nitrosobenzene and aniline by mutual oxidation and reduction (dismutation), and from the former, as before, azoxybenzene is formed.

$$2\,\phi \cdot NHOH \longrightarrow \phi \cdot NO + \phi \cdot NH_2 + H_2O$$
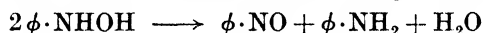
Phenylhydroxylamine will condense with aldehydes, but not with ketones, to give N-phenyl ethers of oximes:

$$\phi \cdot CHO + HO \cdot NH\phi \longrightarrow \phi \cdot \underset{\underset{O \diagup \overset{N}{\diagdown} \phi}{\|}}{CH}$$
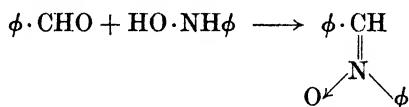
With phenyl magnesium bromide, phenylhydroxylamine gives triphenyl hydrazine.[1] This reaction appears to take the following course; diphenylamine is first formed by a reaction similar to the formation of aniline from phenyl magnesium bromide and hydroxylamine itself.[2] The diphenyl-

$$\phi \cdot MgBr + NH_2OH \longrightarrow \phi \cdot NH_2 + Mg(OH)Br$$
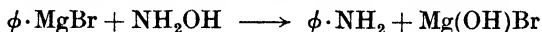
amine, or more probably its magnesium derivative, then reacts with unchanged phenylhydroxylamine:[3]

$$\phi_2NMgBr + HONH \cdot \phi \longrightarrow \phi_2N \cdot NH\phi + Mg(OH)Br.$$
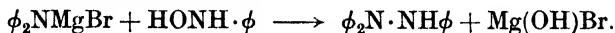
When phenylhydroxylamine decomposes in acid solution a large variety of products is formed according to the conditions chosen. With dilute sulphuric acid p-amino-phenol is practically the sole product, but with alcoholic hydrogen chloride, p-chloraniline, o-chloraniline, p-phenetidine $(EtO \cdot C_6H_4 \cdot NH_2)$, o-phenetidine, aniline, azoxybenzene, and p-amino-phenol are all formed.[4] These decompositions have been minutely studied by Bamberger,[5] who has shown that the decompositions are closely paralleled by those of phenyl azide, ϕN_3. He thus finds support for the suggestion that he had made earlier, that the primary product of decomposition is the radical $\phi \cdot N\!\!<$, which can be a common term in both

[1] M. Busch and R. Hobein, *Ber.* 1907, **40**, 2099.
[2] A. Weissberger, K. Fusold, and H. Bach, *J. pr. Chem.* 1930, **124**, 29.
[3] See E. Bamberger, *Annalen*, 1921, **424**, 286.
[4] E. Bamberger and J. Lagutt, *Ber.* 1898, **31**, 1503.
[5] Summarizing papers, *Annalen*, 1921, **424**, 233, 297; 1925, **441**, 207.

decompositions, coming from the hydroxylamine by loss of water and from the azide by loss of nitrogen. The alternative explanation of the similarity,[1] that the hydroxylamine is an intermediate product in the azide decomposition, formed by a reaction such as

$$\phi \cdot N_3 + H_2O \longrightarrow \phi \cdot NHOH + N_2,$$
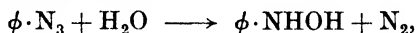
is ruled out by the fact that when the hydroxylamine decomposes, azoxy compounds are almost always formed to some extent, but these compounds never occur among the decomposition products of the azide. The radical can react with the acid or the solvent, or can rearrange and polymerize in a variety of ways and thus give rise to the multiplicity of products. The radical hypothesis provides the most satisfactory explanation for the formation of these products. For example, if aniline is added, p-amino-diphenylamine is found in considerable quantity, and this could well be formed by the interaction of the aniline and the radical.

Again if the decomposition takes place in alcoholic sulphuric acid, the ethyl ethers of amino-phenols are formed, although the amino-phenols themselves are not converted into their ethers by alcoholic sulphuric acid, and are thus unlikely to be intermediate products: and the radical may well combine directly with the solvent to give the ethers.
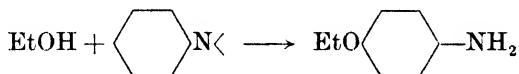
Bamberger's hypothesis that the radicals are the true intermediates in these decompositions receives strong support from the observations of S. Goldschmidt on the oxidation of aniline (p. 54), where there is direct evidence that analogous radicals can exist.

The chief interest in the di-substituted arylhydroxylamines lies in their behaviour on oxidation. The N,N-dibenzyl derivative can be obtained by the interaction of benzyl chloride and hydroxylamine in the presence of sodium carbonate; its O-benzoyl compound is formed by a curious reaction between dibenzylamine and benzoyl peroxide in boiling ether:[2]

$$(\phi CH_2)_2NH + (\phi \cdot CO)_2O_2 \longrightarrow (\phi CH_2)_2NO \cdot CO\phi + \phi CO_2H.$$
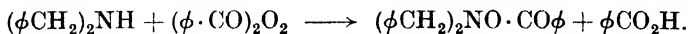
At higher temperatures this benzoyl derivative decomposes into benzoic acid and the Schiff's base, benzylidene-benzylamine.

$$(\phi CH_2)_2NO \cdot CO\phi \longrightarrow \phi CO_2H + \phi CH:NCH_2\phi$$
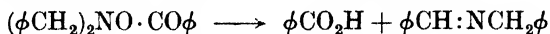
Dibenzylhydroxylamine is readily oxidized by most oxidizing agents to the N-benzyl ether of benzaldoxime:
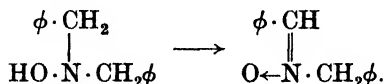
[1] P. Friedländer and M. Zeitlin, *Ber.* 1894, **27**, 197.
[2] S. Gambarjan, *Ber.* 1925, **58**, 1775; 1927, **60**, 390.

N,N-diphenylhydroxylamine behaves on oxidation in a startlingly different fashion from the dibenzyl compound. The diphenyl compound can be obtained by the action of phenyl magnesium bromide on nitrosobenzene at $-15°$ in ether.[1] The reaction may be represented by the equation

$$\phi \cdot NO + \phi MgBr \longrightarrow \phi_2 N \cdot OMgBr \longrightarrow \phi_2 NOH$$
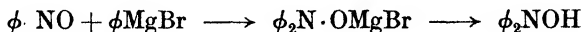
It is more complicated than this, since diphenylamine and diphenyl are always among the products.[2] Diphenylhydroxylamine is an unstable substance (m.p. 60°), decomposed by light and most reagents. When oxidized with silver oxide, the molecule loses one atom of hydrogen and the product has the composition and molecular weight corresponding to the formula $\phi_2 NO$. It thus contains nitrogen in neither of the valency states usual in organic compounds, but tetravalent as in nitrogen peroxide, NO_2. The compound is dark red, and liberates iodine from dilute aqueous hydriodic acid, and thus resembles NO_2 in some properties. On the other hand, nitrogen peroxide polymerizes at low temperatures to N_2O_4, but this compound is monomolecular in solution even at $-70°$. It is readily reduced to diphenylamine. The constitution of this curious compound, diphenyl nitric oxide, is confirmed by the properties of an analogous substance. If phenylhydroxylamine is allowed to react with acetone at room temperature, a condensation product is obtained which has been shown by the careful investigation of F. H. Banfield and J. Kenyon[3] to be the N-phenyl ether of the oxime of a ketonic hydroxylamine and to have the structure:

$$Me_2C—CH_2—C \cdot Me$$
$$\phi \cdot NOH \quad \phi \cdot N{\rightarrow}O$$
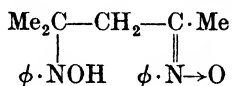
This compound resembles N, N-diphenylhydroxylamine in that it contains a hydroxylamine group in which both N-hydrogen atoms are replaced by tertiary carbon, and it is oxidized by silver oxide to lose one hydrogen atom from the hydroxyl group and give a bright red product containing tetravalent nitrogen. The nature of the compound is very clearly shown by the fact that it is paramagnetic.[4] Compounds containing carbon, hydrogen, oxygen, and nitrogen are, of course, almost all diamagnetic, since of necessity they contain an even number of electrons whose spins neutralize one another (molecular oxygen, with 16 electrons, is an exception). A compound of the type R_2NO must have an odd number and, in fact, the compound has a magnetic moment which corresponds very closely to the value predicted for one unpaired electron. The compound is thus a free radical, but, unlike the free radicals formed in the spontaneous dissociation of hexaphenylethane and tetraphenylhydrazine (see p. 388),

[1] H. Wieland and A. Roseeu, *Ber.* 1912, **45**, 494; Wieland and M. Offenbächer, ibid. 1914, **47**, 2111.

[2] H. Gilman and R. McCracken, *J. Amer. C. S.* 1927, **49**, 1052.

[3] *J.C.S.* 1926, 1612.

[4] J. Kenyon and S. Sugden, ibid. 1932, 170.

it shows no tendency to associate to a bimolecular substance. Diphenyl nitric oxide can be regarded as the amine oxide of the radical from tetra-phenylhydrazine, while the aminium salts already mentioned (p. 63) are its quaternary derivatives.

$$NMe_3 \qquad Me_3N{\to}O \qquad [NMe_4]Br$$
Trimethylamine $\qquad$ amine oxide $\qquad$ quaternary bromide

$$N\phi_2 \qquad \phi_2N{\to}O \qquad [N\phi_3]Br$$
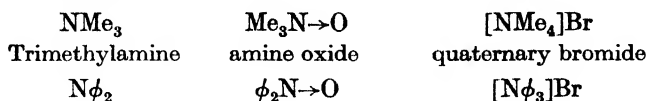
Introduction of substituents into the phenyl rings of the simple carbon and nitrogen radicals has a profound effect on the stability of the radicals. There is a similar effect with radicals of the diphenyl nitric oxide type; the p, p'-dinitro compound is more stable than the unsubstituted radical, and the corresponding dimethyl derivative is very much less stable.[1] The reasons which underlie the existence of these radicals when aryl groups are directly attached to the nitrogen atom, but not when a saturated carbon atom is interposed as in the dibenzyl compound, are almost certainly the same as with the simple carbon and nitrogen radicals. They are briefly discussed below (p. 390).

THE AMINE OXIDES

These compounds may be regarded as derivatives of the tautomeric form of hydroxylamine $H_3N{\to}O$.[2] They are closely related to the tertiary amines from which they can be obtained by oxidation. Certain members of this class, such as trimethylamine oxide, occur naturally, notably in the muscles of fish.[3] The first amine oxide known was prepared by W. R. Dunstan and E. Golding[4] by the action of methyl iodide on hydroxylamine. The product is the hydriodide of trimethylamine oxide, $[NMe_3OH]I$, which with alkali gives the free base in its hydrated form. The triethyl compound can be obtained similarly, but with propyl and isopropyl iodides the reaction stops at the stage of the dialkylhydroxylamine, $Pr_2N \cdot OH$.

A more useful and general method, applicable both in the aliphatic and aromatic series, is the oxidation of a tertiary amine. For aliphatic compounds dilute aqueous hydrogen peroxide (3 per cent.) gives almost quantitative yields of the amine oxide after standing at room temperature for 24 hours.[5] Evaporation of the solution under reduced pressure leaves the hydrated amine oxide; thus from trimethylamine the product is $Me_3NO, 2H_2O$. In the aromatic series hydrogen peroxide and Caro's (per-monosulphuric) acid can be used,[6] but the best reagent is perbenzoic acid, $\phi \cdot CO \cdot OOH$, which can be obtained from benzoyl peroxide. A tertiary amine, such as dimethylaniline, is dissolved in benzene and the perbenzoic

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[1] H. Wieland and K. Roth, *Ber.* 1920, **53**, 210.

[2] F. Haber, *Ber.* 1896, **29**, 2444.

[3] See R. Kapeller-Adler and J. Krael, *Biochem. Z.* 1930, **224**, 364.

[4] *J.C.S.* 1899, **75**, 792, 1004.

[5] Dunstan and Golding, loc. cit.; J. Meisenheimer, *Annalen*, 1913, **397**, 286.

[6] E. Bamberger, *Ber.* 1899, **32**, 342.

acid is added; the oxidation is complete after 10 minutes and the amine oxide can be precipitated as its picrate by adding picric acid.[1]

Trimethylamine oxide is an extremely hygroscopic solid melting at 208°. The hydrate contains two molecules of water which are very difficult to remove without decomposition of the base. The removal is best carried out by heating under 10 mm. pressure at 120–150°, and subliming the anhydrous base at 180°.[2] The aromatic compounds are also hygroscopic solids but do not appear to form definite hydrates; they are very soluble in water, alcohol, benzene, and chloroform, but not in ether or ligroin. Amine oxides can easily be reduced to tertiary amines by reagents such as tin and hydrochloric acid; unlike many hydroxylamine derivatives they do not reduce Fehling's solution. The amine oxides decompose on heating, usually before melting and some even on standing at room temperature. From an aliphatic compound or one of its salts the usual products of decomposition are an aldehyde and a secondary amine:

$$(CH_3)_3NO \longrightarrow (CH_3)_2NH + CH_2O.$$
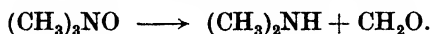
The aromatic compounds give a large variety of products on thermal decomposition,[3] among which is usually the tertiary amine formed by simple loss of oxygen. Certain amine oxides have their own characteristic modes of decomposition. Thus methylallylaniline oxide,

$$CH_2:CH \cdot CH_2 \cdot N\phi Me \rightarrow O,$$

rearranges, especially in the presence of alkali, to N-methyl-O-allyl-N-phenylhydroxylamine, $\phi NMe \cdot OCH_2 \cdot CH:CH_2$, by migration of the allyl group from nitrogen to oxygen.[4] This reaction is restricted to the allyl derivatives and is connected with the abnormal ease with which the allyl group can migrate, as in the rearrangement of allyl ethers of phenols.[5] Certain cyclic amine oxides containing a ten-membered ring rearrange in another way; when they are heated with acetic and hydrochloric acids the oxygen atom migrates as shown to form a ketone.[6] This reaction has rendered possible the synthesis of the alkaloids cryptopine and protopine by the rearrangement of the amine oxides of certain berberine derivatives.
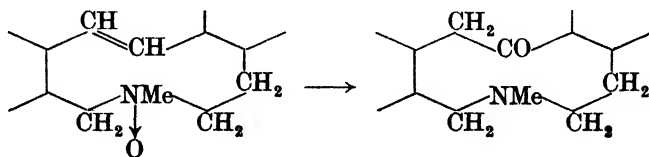
The aromatic and aliphatic amine oxides are bases. The structure of

[1] J. Meisenheimer, *Annalen*, 1926, **449**, 199.

[2] J. Meisenheimer, ibid. 1903, **397**, 286.

[3] E. Bamberger and P. Leyden, *Ber.* 1901, **34**, 12.

[4] J. Meisenheimer, *Ber.* 1919, **52**, 1667.

[5] L. Claisen, *Annalen*, 1919, **418**, 69.

[6] R. D. Haworth and W. H. Perkin, *J.C.S.* 1926, **445**, 1769.

their salts is most clearly shown by the fact that the methiodide of tri-methylamine oxide is identical with that of trimethylhydroxylamine.[1]

$$Me_3N \rightarrow O + MeI \longrightarrow [Me_3N \cdot OMe]I \longleftarrow Me_2N \cdot OMe + MeI$$
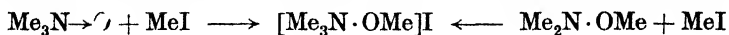
This is conclusive proof that in the methiodide of the amine oxide one methyl group is attached to oxygen, and it follows that the constitution of the salt of an amine oxide with the acid is $[R_3NOH]X$.

Aqueous solutions of amine oxides might then be expected to contain the base $[R_3NOH]OH$, which on the analogy of the quaternary ammonium hydroxides might be a strong base. Such solutions do not, however, behave as though they contained a strong electrolyte, and differ in a striking fashion from solutions of the quaternary bases derived from the related hydroxylamines $[R_3N \cdot OAlk]OH$. T. D. Stewart and S. Maeser[2] prepared the compounds $[Me_3N \cdot OMe]I$ and $[Me_3N \cdot OEt]I$ by the action of the appropriate alkyl iodide on anhydrous trimethylamine oxide at a low temperature. Aqueous solutions of either of these salts together with the equivalent of caustic potash showed a conductivity equal to the sum of the two substances separately. Hence the bases from which these salts are derived are strong electrolytes, and there is no tendency in dilute solution for the ions $[R_3N \cdot OAlk]^+$ and OH^- to associate with the formation of an undissociated molecule. The salts of trimethylamine oxide, such as $[Me_3N \cdot OH]I$, behave quite differently; in solution they show an acid reaction, and indicator measurement of the extent to which they suffer salt hydrolysis shows that the base from which they are derived has a very small dissociation constant of the order of 10^{-10}: in aqueous solution it exists almost entirely as undissociated molecules. This enormous differ-ence in basicity between the two hydroxides, which was predicted by G. N. Lewis, is exactly parallel with that between tetramethyl-ammonium hydroxide and the hydroxide derived from trimethylamine, which has been discussed in detail above (p. 30). There must be a possibility of union between the kation of the amine oxide and the hydroxyl ion to form an undissociated molecule which is absent in the quaternary hydroxyl-amine kation. This must arise from the presence of a hydrogen atom attached to the oxygen in the kation of the weak base, since that is the only difference between the two ions, and the hydroxyl anion must become linked to this hydrogen atom by a co-ordinate bond (for the nature of the co-ordinate link to hydrogen see the Introduction). The dissociation of the weakly basic amine oxide is thus best represented as follows, the equilibrium lying well over to the left-hand side,

$$R_3\overset{+}{N}OH\cdots OH^- \rightleftharpoons [R_3 \cdot NOH]^+ + OH^-.$$
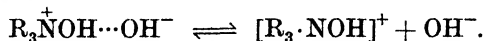
The resolution of certain amine oxides which contain three different hydrocarbon radicals, $RR'R''NO$, has been discussed above (p. 34). Since nitrogen never seems to show a covalency of five the constitution

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[1] L. W. Jones and R. T. Major, *J. Amer. C. S.* 1928, **50**, 2742.

[2] *J. Amer. C. S.* 1924, **46**, 2583.

of the amine oxides is best represented by the formula $R_3N \rightarrow O$, and not by the older formula $R_3N = O$. The distinction between the four covalencies of a nitrogen atom and the fifth ionizable group is well shown by the behaviour of two compounds closely related to those which have been discussed. Meisenheimer[1] prepared the hydroxide $[Me_3N \cdot OMe]OH$ by the action of caustic soda on the methiodide of trimethylamine oxide, and also the methoxide $[Me_3N \cdot OH]OMe$, by treating trimethyl-hydroxylamine hydriodide with sodium methoxide. If all the nitrogen valencies were the same, these two compounds would be identical. They are, however, perfectly distinct and each decomposes in its own fashion, the first into trimethylamine, formaldehyde, and water, and the second into trimethylamine oxide and methyl alcohol:

$$[Me_3N \cdot OCH_3]OH \longrightarrow Me_3N + CH_2O + H_2O$$

$$[Me_3N \cdot OH]OMe \longrightarrow Me_3N \rightarrow O + MeOH.$$
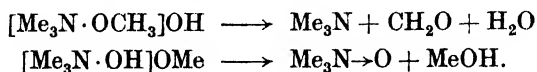
THE OXIMES

The oximes are compounds containing the group $>C = NOH$. The name was introduced by Victor Meyer and implies the structure, being a contracted form of oxy-imine. Some members of this class are often described as isonitroso compounds, but there is no difference in structure or reactions between isonitroso compounds and oximes. The prefix isonitroso implies that the compounds can be regarded as isomers of true primary or secondary nitroso compounds, $RCH_2 \cdot NO$ or $R_2CH \cdot NO$. Save in exceptional cases such nitroso compounds do not exist, but pass completely into the isonitroso form. The behaviour is quite different from that of the primary and secondary nitro compounds (see p. 231), where there is an equilibrium between nitro and isonitro species in which the former predominates. The use of the term isonitroso tends to cause confusion; it is falling into disuse, its place being taken by the prefix oximino.

The first compound of this class to be recognized was oximino-(isonitroso-)acetone, $CH_3 \cdot CO \cdot CH : NOH$, which Victor Meyer and J. Züblin described in 1878.[2] There are two general methods for preparing oximes. The first is by the action of hydroxylamine on aldehydes and ketones:

$$\begin{array}{c} R \\ \diagdown \\ R' \diagup \end{array} CO + H_2NOH \longrightarrow \begin{array}{c} R \\ \diagdown \\ R' \diagup \end{array} C : NOH + H_2O.$$
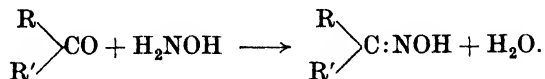
Because of this reaction the oximes can be regarded as derivatives of aldehydes and ketones and are conveniently divided into the two classes of aldoximes and ketoximes, according to whether their structure is $RCH : NOH$ or $\begin{array}{c} R \\ R' \end{array} \!\!>\!\! C : NOH$. The ease with which this reaction takes place varies widely with the aldehyde or ketone involved. In general aldehydes react more readily than ketones, and the aliphatic ketones more readily

[1] *Annalen*, 1913, 397, 273.　　　　[2] *Ber.* 11, 695.

than the aromatic. The oxime of an aliphatic ketone such as acetone can be prepared by shaking the ketone with the equivalent of hydroxylamine in water at r,om temperature, the product being separated by ether extraction. The same is true for aromatic aldehydes, though it is often better to add excess of free caustic soda. For aromatic ketones it is usually necessary to boil an alcoholic solution of the ketone with the equivalent of hydroxylamine hydrochloride together with excess of sodium acetate.

The velocity of oxime formation, particularly that of acetoxime, has been frequently measured, under a variety of conditions, and has been shown to be much influenced by the hydrogen ion concentration of the solution.[1] The reaction between hydroxylamine and acetone is dimolecular and reversible; the rates of formation and of hydrolysis of the oxime both vary with the hydrogen ion concentration, but in a different manner. The rate of formation is greatest at p_H 4·7, while that of hydrolysis is greatest at p_H 2·3, and is hardly detectable at values of $p_H > 5$. Hence, as W. Hückel and M. Sachs[2] have pointed out, the most favourable conditions for oxime preparation are to use a solution containing sodium acetate and acetic acid, which buffer the solution to the most favourable hydrogen ion concentration. In the presence of much free alkali the reaction again becomes rapid, but cannot be followed quantitatively because of the instability of free hydroxylamine in strongly alkaline solution: it seems probable that under these conditions the mechanism of the reaction is entirely different and that the anion $NH_2 \cdot O^-$ is involved.

The formation of an oxime is sometimes used as a test for the presence of a carbonyl group in a compound of unknown structure, and the determination of the melting-point of its oxime as a method of identifying an aldehyde or ketone. Since, however, oximes do not always form rapidly and their purification is sometimes difficult, it is usually more convenient to use as reagent semicarbazide, phenylhydrazine or a substituted phenylhydrazine (see pp. 287 and 394).

Compounds containing more than one carbonyl group can obviously react with more than one equivalent of hydroxylamine. The best-known class of dioximes are those derived from 1,2-diketones and ketonic aldehydes ($R \cdot CO \cdot CO \cdot R'$). An example of such compounds is dimethylglyoxime, $MeC(:NOH) \cdot C(:NOH)Me$ (the name derives from the dialdehyde glyoxal, $HCO \cdot CHO$), which is used as a quantitative reagent for nickel. Such diketones usually react with great ease to form a monoxime: benzil ($\phi \cdot CO \cdot CO \cdot \phi$), for example, gives α-benzilmonoxime rapidly at $-5°$ in the presence of concentrated sodium hydroxide. The second oxime group is not introduced so readily, and to obtain the dioxime, the ketone must be heated in solution with excess of hydroxylamine.

β-Diketones do not in general give oximes with hydroxylamine, but

[1] A. Ölander, Z. phys. Chem. 1927, 129, 1; see also E. Barrett and A. Lapworth, J.C.S. 1908, 93, 85; S. F. Acree, Amer. Chem. J. 1908, 39, 300.

[2] Annalen, 1932, 498, 166.

are converted by loss of two molecules of water into isoxazoles.[1] Similarly β-ketonic esters, such as acetoacetic ester, give isoxazalones, losing a molecule of water and one of alcohol:

$$R \cdot CO \cdot CH_2 \cdot CO \cdot R' \longrightarrow \underset{\underset{NOH}{\|}}{R \cdot C} \cdot CH_2 \cdot CO \cdot R' \longrightarrow$$

$$CH_3 \cdot \underset{\underset{NOH}{\|}}{C} \cdot CH_2 \cdot CO_2Et \longrightarrow$$
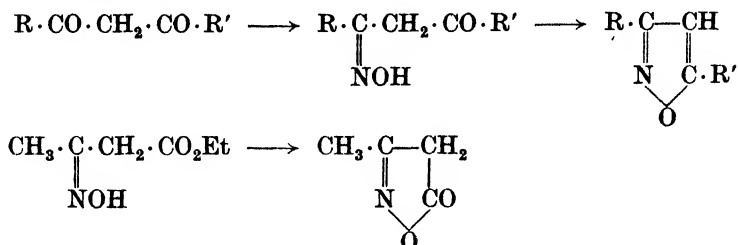
The second general method for the preparation of oximes is by the action of nitrous acid or one of its esters upon a compound containing a reactive methyl or methylene group, as, for example, a methylene ketone. The reaction can be written formally as:

$$R \cdot CO \cdot CH_2 \cdot R' + O:NOH \longrightarrow R \cdot CO \cdot C(:NOH) \cdot R' + H_2O.$$
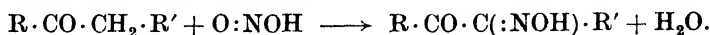
There is little doubt, however, that it is the enolic form of the ketone which enters into reaction. It was by a reaction of this type that Victor Meyer obtained the first known oxime. The reaction proceeds, in general, with the greater ease the larger the proportion of the ketone present in the enolic form. A β-diketone such as benzoyl-acetone ($\phi \cdot CO \cdot CH_2 \cdot CO \cdot Me$), of which the solid form is the pure enol, reacts rapidly with free nitrous acid at 0° in glacial acetic solution to give oximinobenzoylacetone, $\phi \cdot CO \cdot C(:NOH) \cdot CO \cdot Me$.[2] A β-ketonic ester, such as acetoacetic ester, behaves similarly; if, however, such an ester is dissolved in aqueous caustic soda and left to stand, it is hydrolysed to the sodium salt of the β-ketonic acid: addition of sodium nitrite followed by dilute mineral acid gives the oximino ketonic acid, which immediately loses carbon dioxide to form an oximino ketone. By this method oximino-acetone can be easily prepared from acetoacetic ester.[3]

Ketones which are not β-diketones or β-ketonic esters do not react with nitrous acid with such ease, and it is necessary to use one of the two methods first described by L. Claisen and O. Manasse.[4] In both methods the ketone reacts with an ester of nitrous acid in the presence of a catalyst. In the first method the catalyst is sodium ethoxide and the ester freshly prepared amyl nitrite. The ketone and its equivalent of sodium ethoxide are dissolved in alcohol and the equivalent of nitrous ester added at a low temperature: after 24 hours or more, the product can be separated by dilution with water, extraction of alkali-insoluble compounds with ether, and precipitation of the oximino compound by addition of mineral acid or carbon dioxide. The second method is similar except that hydrogen chloride is used as catalyst. Methyl and ethyl nitrites, which are gases at room temperature, have been used in the place of the amyl ester, and

[1] L. Claisen, *Ber.* 1891, **24**, 3900.   [2] L. Wolff, *Annalen*, 1902, 325, 136.
[3] G. Charrier, *Gazz.* 1907, **37**, ii. 145.   [4] *Ber.* 1887, **20**, 656. 2194.

their reaction is somewhat more rapid:[1] their use suffers in some cases from the disadvantage that it is not so easy to use them in accurately determined amount, while amyl nitrite is a liquid which can be weighed. Excess of nitrous ester is to be avoided since it can react with the oximino ketone to give nitrous oxide:[2]

$$R \cdot CO \cdot C(:NOH) \cdot R' + EtONO \longrightarrow R \cdot CO \cdot CO \cdot R' + N_2O + EtOH.$$
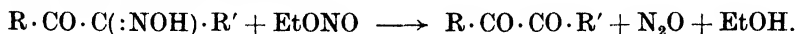
Many ketones give equally good yields with either catalyst, but in some cases there are marked differences.

There are a few other reactions of minor importance which lead to the formation of oximes. One of the more curious is a modified Friedel-Crafts reaction:[3] mercuric fulminate reacts with benzene in the presence of partially hydrated aluminium chloride to give 70 per cent. of the theoretical amount of benzaldoxime. If anhydrous aluminium chloride is used the main product is benzonitrile, $\phi \cdot C:N$; the reasons for this are discussed later (p. 341).

$$CNOH \longrightarrow \underset{H}{\overset{Cl}{>}}C:NOH \longrightarrow \phi CH:NOH$$
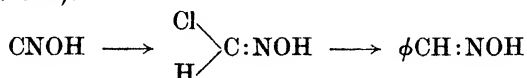
The simplest oxime, formaldoxime, $H_2C:NOH$, is a liquid boiling at 84°, which goes over into a trimolecular polymer with great ease. Some aliphatic ketoximes are liquid, but the majority of oximes are solid at room temperature. The lower members, such as acetoxime and benzaldoxime, boil without decomposition: some are soluble in water, but can be extracted from aqueous solution with ether. The oximes behave both as weak acids and as weak bases, giving rise to salts of the types $[RCH:NO]Na$ and $[RCH:NHOH]Cl$. They are soluble in aqueous caustic alkalis, but are precipitated from such solution by carbon dioxide; the acidic dissociation constants of a series of aromatic aldoximes have been measured by O. L. Brady and R. F. Goldstein,[4] and all lie between 10^{-10} and 10^{-12}, while that of carbonic acid is 3×10^{-7}. As bases the oximes are very weak and their hydrochlorides are extensively hydrolysed in aqueous solution. From the measurements recorded, their basic dissociation constants appear to be of the order 10^{-12}. Oximes can be hydrolysed by mineral acids to hydroxylamine and the related aldehyde or ketone, but are not attacked by caustic alkalis. They can be reduced to amines ($>C:NOH \longrightarrow >CHNH_2$) by a variety of methods, of which the more important are electrolytic reduction in cooled sulphuric acid with electrodes of lead or mercury[5] and reduction with sodium amalgam in alcoholic solution.[6]

In virtue of the hydroxyl group which they contain, the oximes give acyl derivatives with acid chlorides and anhydrides:

$$>C:NOH \longrightarrow >C:N \cdot O \cdot CO \cdot R.$$
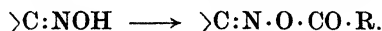
[1] W. K. Slater, *J.C.S.* 1920, **117**, 587. [2] O. Manasse, *Ber.* 1888, **21**, 2176.
[3] R. Scholl, *Ber.* 1899, **32**, 3496. [4] *J.C.S.* 1926, **129**, 1923.
[5] J. Tafel and E. Pfeffermann, *Ber.* 1902, **35**, 1515.
[6] See Houben-Weyl, *Die Methoden der organischen Chemie*, 3rd ed., vol. ii, p. 350.

These substances have, naturally, lost the acidic and basic properties of the oximes themselves; they are hydrolysed to the oxime by aqueous alkalis and acids, usually with great ease. With the aldoximes, in which there is a hydrogen atom attached to the carbon atom carrying the oximino group, vigorous treatment with an acid chloride or anhydride leads to dehydration and the formation of a nitrile:

$$RCH:NOH \longrightarrow RCN + H_2O.$$
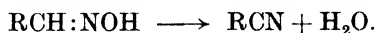
Under milder conditions acyl derivatives of some aldoximes can be obtained,[1] but many aliphatic aldoximes are dehydrated under all conditions and their acyl derivatives are unknown. As is discussed more fully below, the acetyl derivatives of certain aldoximes behave in an unexpected way towards aqueous alkalis and alkaline carbonates and, instead of undergoing hydrolysis, are converted into nitriles:

$$R \cdot CH:N \cdot O \cdot COCH_3 \longrightarrow R \cdot CN + CH_3 \cdot CO_2H.$$
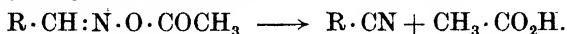
By the action of alkylating agents an oxime can be converted into its alkyl ether: the reagent most commonly employed is dimethyl sulphate in the presence of caustic soda; alkyl iodides, either alone or with potassium carbonate or silver oxide, are also used. On methylation an oxime usually gives a mixture of two products. In one of these the methyl group is attached to oxygen, as is shown by its hydrolysis to ketone (or aldehyde), hydroxylamine, and methyl alcohol, and such a compound is called the O-methyl ether. The other product is hydrolysed to ketone (or aldehyde) and N-methylhydroxylamine, $NHMe \cdot OH$, and hence must have the methyl group attached to nitrogen: it is called the N-methyl ether. The two ethers can be separated with ease because the N-ether is almost insoluble in ordinary ether or cold petroleum ether, while the O-ether is readily soluble.[2] When they were first prepared the N-ethers were assigned the cyclic structure (I). This structure has been displaced by the 'nitrone' structure (II), for the following reasons.

$$\text{I.} \quad \begin{array}{c} R \\ R' \end{array}\!\!>\!\!C\!<\!\!\begin{array}{c} N \cdot Me \\ | \\ O \end{array} \qquad \text{II.} \quad \begin{array}{c} R \\ R' \end{array}\!\!>\!\!C\!=\!N\!<\!\!\begin{array}{c} O \\ Me \end{array}$$
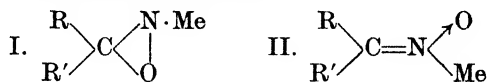
(a) The molecular refractivities of certain N-ethers have been measured by K. von Auwers and B. Ottens[3] and the values obtained agree much more closely with those to be expected from the nitrone structure than from the other.

(b) In some cases two geometrically isomeric N-ethers are known, a point discussed more fully below. With the nitrone structure these can readily be accounted for (III and IV),

$$\text{III.} \quad \begin{array}{c} R \cdot C \cdot R' \\ \| \\ Me \cdot N \rightarrow O \end{array} \qquad \text{IV.} \quad \begin{array}{c} R \cdot C \cdot R' \\ \| \\ O \leftarrow N \cdot Me \end{array}$$
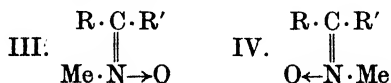
but on the cyclic formula the isomerism must arise from the space-arrange-

[1] A. Hantzsch, *Ber.* 1891, **24**, 37.
[2] L. Semper and L. Lichtenstadt, ibid. 1918, **51**, 928.   [3] Ibid. 1924, **57**, 446.

ment of the groups attached to a saturated trivalent nitrogen atom (V and VI). Such an explanation is extremely improbable, since no compounds

$$\text{V.} \quad \begin{matrix} R \\ R' \end{matrix} \!\!>\!\! C\!\!\underset{}{\overset{O}{\diagup\diagdown}}\!\! N\!\!\diagup^{Me} \qquad\qquad \text{VI.} \quad \begin{matrix} R \\ R' \end{matrix} \!\!>\!\! C\!\!\underset{}{\overset{O}{\diagup\diagdown}}\!\! N\!\!\diagdown_{Me}$$
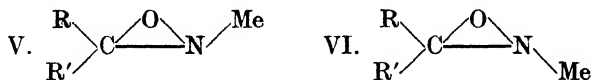
of comparable structure, with a cyclic trivalent nitrogen atom, show geometrical isomerism.[1]

(c) The measurements of L. E. Sutton and T. W. J. Taylor[2] show that the N-methyl ether grouping has a large electric moment. This is most easily understood on the nitrone formula which involves a co-ordinate link between nitrogen and oxygen, since such a link practically always gives rise to a large moment.[3]

(d) If the cyclic formula is correct, an N-ether such as (I), where R and R' are different groups, should be capable of resolution into optical antimers because it contains an asymmetric carbon atom. J. Scheiber[4] attempted to resolve the N-benzyl oxime of opianic acid (VII), and H. Lindemann and Kou-Tschi Tschang[5] the N-methyl ether of p-dimethyl-aminobenzaldoxime (VIII). In neither case was there any indication of resolution.

$$\text{VII. MeO}\!\!\left\langle\begin{array}{c}\\ \\ \end{array}\right\rangle\!\!\text{CH:NBz}\!\to\!\text{O} \qquad \text{VIII. Me}_2\text{N}\!\!\left\langle\begin{array}{c}\\ \\ \end{array}\right\rangle\!\!\text{CH:NMe}\!\to\!\text{O}$$

$$\text{MeO} \quad \text{CO}_2\text{H}$$
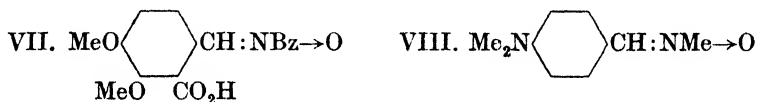
The N-ethers of oximes are weakly basic, in contrast to the O-ethers which show no basic properties at all, a fact which can be used for separating the two types. They are usually less resistant to hydrolysis by acids and melt at a markedly higher temperature than the isomeric O-ethers.

The formation of two ethers raises the question of the structure of the oximes themselves. As will be realized, most of their properties support the formula $>$C:NOH, but it has often been suggested[6] that in solution an oxime is a tautomeric mixture of this form and the nitrone form: $>$C:NOH $\rightleftharpoons$ $>$C:NH$\to$O. If this is so, the equilibrium must lie very much on the side of the hydroxy form, because the absorption spectra in the ultra-violet of an oxime and its O-methyl ether resemble one another very closely, while the N-methyl ether shows an entirely different absorption. There is no need to assume the presence of the nitrone form to account for methylation to an N-ether: a reaction mechanism of the following type is quite probable:

$$>\text{C:NOH} \xrightarrow{\text{Me}_2\text{SO}_4} >\text{C}\!\!=\!\!\underset{\overset{\mid}{\text{Me}}}{\text{NOH}}[\text{MeSO}_4] \longrightarrow >\text{C:NMe}\!\to\!\text{O} + \text{MeHSO}_4.$$

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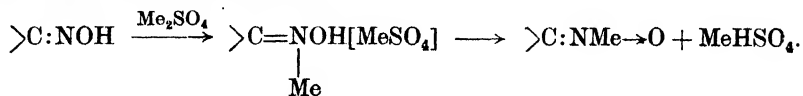
[1] See W. H. Mills, J. D. Parkin, and W. J. V. Ward, *J.C.S.* 1927, 2613.
[2] Ibid. 1931, 2190.
[3] Cf. J. DeVries and W. H. Rodebush, *J. Amer. C. S.* 1931, **53**, 2888.
[4] *Ber.* 1911, **44**, 761.   [5] Ibid. 1927, **60**, 1725.
[6] e.g. O. L. Brady, *J.C.S.* 1916, **109**, 659.

The most interesting point that arises in connexion with the oximes is the stereoisomerism which many of them show and which is the classical example of geometrical isomerism among the nitrogen compounds.

In 1883 H. Goldschmidt[1] found that the dioxime of benzil,

$$\phi \cdot C(:NOH) \cdot C(:NOH) \cdot \phi,$$
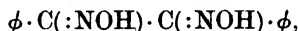
could be obtained in two forms, and in 1889 K. von Auwers and Victor Meyer[2] obtained yet a third form. These three benzildioximes are distinct chemical individuals and not polymorphous or polymeric modifications of one individual; they all have the same molecular weight in solution, and it is of interest to notice that this was one of the first cases in which use was made of Raoult's method for molecular weight determination by the lowering of the freezing-point of a solvent.[3] They are not polymorphs because the difference between them is associated not only with the solid state, e.g. in melting-point and solubilities, but it is maintained in solution where their chemical properties, though similar in some respects, are markedly different in others. Thus, for example, the α-dioxime forms a co-ordination complex with nickel of composition NiR_3 (R represents a molecule of dioxime less one hydrogen atom),[4] the β-dioxime forms no nickel complex at all, and the γ-dioxime one of composition NiR.[5] At the same time all three are benzildioximes, as is shown by the fact that on hydrolysis they give nothing but benzil and hydroxylamine. The α- and γ-dioximes can be converted into the β-dioxime by quite simple means, such as heating in alcoholic solution.

The first explanation of the occurrence of this isomerism was that of V. Meyer and von Auwers. They suggested that if free rotation about the single bond between the two carbon atoms marked with an asterisk

$$\phi \diagdown \overset{*}{C} - \overset{*}{C} \diagup \phi$$
$$\quad \| \quad \|$$
$$NOH \quad NOH$$
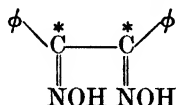
were inhibited for some unknown reason, then the three dioximes might be molecules in which the phenyl and oximino groups attached to one of these carbon atoms were held in different positions with respect to the groups attached to the other carbon atom: conversion of one form into another would involve rotation of one half of the molecule with respect to the other through a certain angle. There was no direct evidence to support this explanation, and it was only advanced because at that time none other seemed possible.

Very soon the discovery by Beckmann[6] that there are two isomeric benzaldoximes, each of formula $\phi CH:NOH$, made any such explanation

[1] *Ber.* **16**, 2176.
[2] Ibid. **22**, 709.
[3] V. Meyer and K. v. Auwers, ibid. 1888, **21**, 813.
[4] L. Tschugaev, *Z. anorg. Chem.* 1905, **46**, 148.
[5] F. W. Atack, *J.C.S.* 1913, **103**, 1317.   [6] *Ber.* 1889, **22**, 1531.

impossible, because this molecule does not contain two singly linked carbon atoms each carrying two different groups, and it became recognized that this isomerism was a property common to a large number of oximes. For some time there was the possibility that the two isomeric forms of an oxime possessed different structures, such as $>C:NOH$ and $>C<^{NH}_{O}$, but this had to be rejected when H. Goldschmidt[1] showed that both reacted with phenyl isocyanate as hydroxylic compounds. The explanation of the isomerism which is accepted to-day was first advanced by A. Hantzsch and A. Werner in 1890.[2]

Cases of geometrical isomerism such as that of maleic and fumaric acids

$$H \cdot C \cdot CO_2H \qquad\qquad H \cdot C \cdot CO_2H$$
$$\|\qquad\qquad\qquad \|$$
$$H \cdot C \cdot CO_2H \qquad\qquad HO_2C \cdot C \cdot H$$

<div align="center">Maleic acid   Fumaric acid</div>
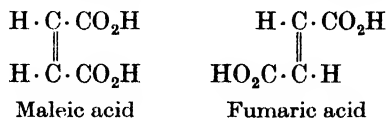
had been recognized by van't Hoff and correctly attributed by him to the fact that, although there is almost universally 'free rotation'[3] about a single bond joining two carbon atoms, 'free rotation' is not possible about a double bond between such atoms, with the result that isomerism such as that indicated by the two formulae above can occur.

What Hantzsch and Werner did was to extend van't Hoff's explanation of the isomerism of such compounds to the oximes. They in fact made two postulates, the first being that there is no 'free rotation' about the link $>C=N-$, and the second that in a molecule containing the group $>C=NOH$, the hydroxyl group is not symmetrically placed with respect to the two different groups R and R'. Two isomeric oximes would on this basis be written:

$$R-C-R' \qquad\qquad R-C-R'$$
$$\|\qquad\qquad\qquad \|$$
$$N \qquad\qquad\qquad N$$
$$\diagdown OH \qquad HO\diagup$$
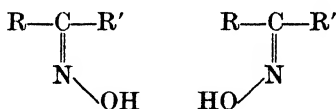
They could advance three weighty reasons in support of their view. Firstly, all the cases where isomerism had been found were either aldoximes, in which the groups R and R' are necessarily different, or else oximes derived from unsymmetrical ketones, whereas no oxime derived from a symmetrical ketone, $R \cdot CO \cdot R$, was known to occur in two forms. This is clearly in accordance with their view, for with the oxime of a symmetrical ketone the two possible configurations are identical. This statement remains true to-day. If it did not hold, clearly there could be no question of geometrical isomerism in the oximes.

Secondly, their view accounted satisfactorily for the existence of three benzildioximes. In such a molecule there are two groupings capable of

[1] *Ber.* 1889, **22**, 3113.   [2] Ibid. 1890, **23**, 11.

[3] A note on free rotation will be found at the end of this chapter.

existing in geometrically isomeric arrangements, so that three, and only three, oximes should exist on the assumptions made; these are:

$$\phi\cdot\underset{\text{HON}}{\text{C}}\!\!-\!\!\underset{\text{NOH}}{\text{C}}\cdot\phi \qquad \phi\cdot\underset{\text{NOH}}{\text{C}}\!\!-\!\!\!-\!\!\!-\!\!\underset{\text{HON}}{\text{C}}\cdot\phi \qquad \phi\cdot\underset{\text{NOH}}{\text{C}}\!\!-\!\!\!-\!\!\underset{\text{NOH}}{\text{C}}\cdot\phi$$
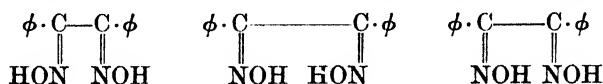
The third argument[1] was based upon the products formed when stereo-isomeric oximes undergo the Beckmann rearrangement. This reaction has already been mentioned on pp. 19 and 49.

E. Beckmann[2] had found that if a ketoxime is treated with certain acidic reagents, of which the most important is phosphorus pentachloride (the oxime being dissolved in dry ether), and the product treated with water, a substituted acid amide is obtained. Thus acetophenone oxime gives acetanilide:

$$\underset{H_3C}{\overset{\phi}{>}}\!\!C\!\!=\!\!NOH \longrightarrow \underset{H_3C}{\overset{HO}{>}}\!\!C\!\!=\!\!N\phi \longrightarrow \underset{H_3C}{\overset{O}{>}}\!\!C\!\!-\!\!NH\phi.$$
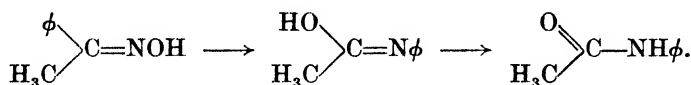
It is clear that a rearrangement has taken place, and that the phenyl group originally attached to a carbon atom has migrated to the nitrogen atom, or rather exchanged in position with the hydroxyl group. The reaction is formally analogous to the Hofmann reaction in which an amide is converted into an amine (see p. 146), and to the Curtius conversion of an acid azide into an isocyanate (see p. 375).

The Beckmann rearrangement will be discussed more fully later; at the moment the point upon which attention should be focused is that with the two isomeric ketoximes of formula $R \cdot C(:NOH) \cdot R'$ the main product of the Beckmann transformation of one oxime is the amide $R \cdot CO \cdot NHR'$, while the other oxime gives as main product $R' \cdot CO \cdot NHR$. The reaction has followed the same course in the two cases, but there is a difference as to which of the two groups, R and R', has been involved in the exchange of position. This is strong evidence for the view that two isomeric oximes have structures of exactly the same type, but differ from one another in the space arrangement of their constituent groups.

Many more facts have since appeared which support geometrical isomerism as the true explanation of oxime isomerism; the accumulated weight of the evidence is now so great that no legitimate doubts as to its truth can exist, in spite of the many points in oxime chemistry which are still obscure. The following three pieces of evidence are, perhaps, the most important.

Any possibility that the isomerism is structural and not geometrical, and that it arises from the position of the hydrogen atom of the oxime group, as, for example, in the forms $>\!C\!\!=\!\!NOH$, $>\!C\!\!=\!\!N\!\!<_H^O$, $>\!C\!\!-\!\!NH$,
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad O$$

[1] Hantzsch, *Ber.* 1891, **24**, 19.

[2] Ibid. 1886, **19**, 988; 1887, **20**, 1507, 2580; 1889, **22**, 516; *Annalen*, 1889, **252**, 1.

a view upheld by F. W. Atack,[1] was removed when it was established that in two cases the two isomeric O-ethers and the two isomeric N-ethers corresponding to a pair of oxime isomers can be obtained. The only formulae that can be allotted to a series such as this are:

$$R \cdot C \cdot R' \qquad\qquad R \cdot C \cdot R'$$
$$\| \qquad\qquad\qquad \|$$
$$NOH \qquad\qquad\quad HON$$

$$\overbrace{R \cdot C \cdot R' \quad R \cdot C \cdot R'}\qquad \overbrace{R \cdot C \cdot R' \quad R \cdot C \cdot R'}$$
$$\| \qquad\quad \| \qquad\qquad \| \qquad\quad \|$$
$$NOMe \quad MeN{\to}O \qquad MeON \quad O{\leftarrow}N \cdot Me$$
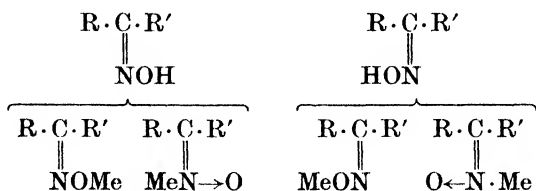
The known cases are the four ethers of p-tolylphenylketoxime,[2]
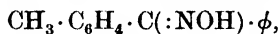
$$CH_3 \cdot C_6H_4 \cdot C(:NOH) \cdot \phi,$$

where three are solids and one O-ether is a colourless oil, and those of p-nitrobenzophenone oxime, $O_2N \cdot C_6H_4 \cdot C(:NOH)\phi$,[3] where all are distinct crystalline solids. Two of these give methylamine with strong hydriodic acid, showing them to be N-ethers, and the two O-ethers give methyl iodide.

One of the most direct demonstrations of the truth of the assumptions of Hantzsch and Werner is afforded by the work of W. H. Mills and A. M. Bain[4] and W. H. Mills and B. C. Saunders.[5] The fundamental idea underlying these ingenious investigations was that, while, on the one hand, there is no simple and unambiguous test whereby it can be decided whether a given case is one of geometrical isomerism or not—the best that can be done is to demonstrate that no other kind of isomerism can be present—, on the other hand, the resolution of a compound into optically active forms can only have one meaning, that the space arrangement of the molecule is enantiomorphous. Mills removed the problem of the configuration in space of the oxime grouping from the region of geometrical isomerism to that of optical isomerism where a successful resolution gives an unequivocal answer. The assumptions of Hantzsch and Werner imply a certain space distribution, and a decisive test can be made by trying to resolve a compound which can only exist in enantiomorphous forms if those assumptions are true. If the resolution is effected, the configuration in space of the oxime grouping is established, and, as a necessary consequence, it has been shown that the arrangement in a molecule of the type $\overset{a}{\underset{b}{\Large>}}C{=}NOH$ is such that geometrical isomerism can exist.

The first compound of the required type investigated was the oxime of $cyclo$-hexanone-4-carboxylic acid.

$$\overset{HO_2C}{\underset{H}{\Large>}}C\overset{CH_2{-}CH_2}{\underset{CH_2{-}CH_2}{\Large<}}\overset{\Large>}{\,}C{=}NOH$$
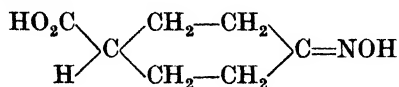
[1] $J.C.S.$ 1921, **119**, 1175.

[2] L. Semper and L. Lichtenstadt, $Ber.$ 1918, **51**, 928.

[3] O. L. Brady and R. P. Mehta, $J.C.S.$ 1924, **125**, 2297; L. E. Sutton and T. W. J. Taylor, ibid. 1931, 2910.   [4] Ibid. 1910, **97**, 1866.   [5] Ibid. 1931, 537.

On the assumptions made by Hantzsch and Werner the arrangement of this molecule in space must be as is shown below (I), and it will not be superposable upon its mirror image (bonds shown in thick lines represent those above the plane of the paper, and those in dotted lines, those below it). If, on the other hand, the hydroxyl group is placed symmetrically with respect to the doubly bound carbon and nitrogen atoms (III), the molecule has a plane of symmetry and resolution would be impossible.
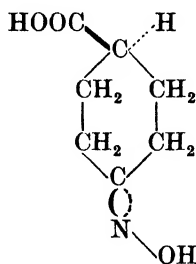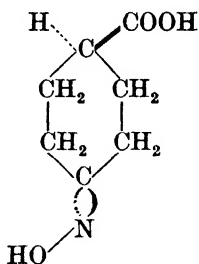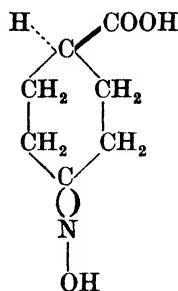
I.   II.   III.

The compound was resolved by means of its salts with quinine and morphine, and in consequence the geometrical isomerism of isomeric oximes receives strong support. The only objection to this argument that can have any force is that the compound may not have the structure allotted to it, but may be the isomeric cyclo-hexenyl-hydroxyl-amine.
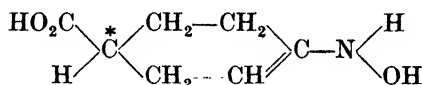
In this case the carbon atom marked with an asterisk is asymmetric and the enantiomorphism has nothing to do with a particular configuration round the nitrogen atom. The compound, however, does not show the strong reducing properties characteristic of N-hydroxylamines, so that this structure is unlikely. To remove all possible doubt, it was clear that a compound should be investigated in which the atoms attached to the carbon atom carrying the oximino group should not be united to hydrogen atoms: in this case no isomeric change of the type

$$-CH_2 \cdot C(:NOH)- \longrightarrow -CH:C(NHOH)-$$
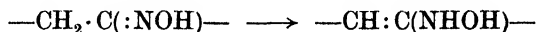
would be possible. Such a compound was prepared by Mills and Saunders:[1] β-methyl-trimethylene dibromide was condensed with sodium trithiocarbonate and the product was heated with the methyl ester of phenylhydrazine o-carboxylic acid: the resulting ester was then hydrolysed to the free acid.

---

[1] Loc. cit.

$$
\begin{array}{ccc}
\underset{\text{BrCH}_2}{\overset{\text{CH}_3}{\diagdown}}\text{C}\underset{\text{CH}_2\text{Br}}{\overset{\text{H}}{\diagup}} & & \underset{\text{H}_2\text{C}}{\overset{\text{CH}_3}{\diagdown}}\text{C}\underset{\text{CH}_2}{\overset{\text{H}}{\diagup}} \\
+ & \longrightarrow & \\
\underset{\text{NaS}}{}\overset{\text{SNa}}{\diagdown}\text{C} & & \\
\parallel & & \\
\text{S} & & \text{S}
\end{array}
$$

(Structures with) $N \cdot NH \cdot C_6H_4 \cdot CO_2Me$ $N \cdot NH \cdot C_6H_4 \cdot CO_2H$
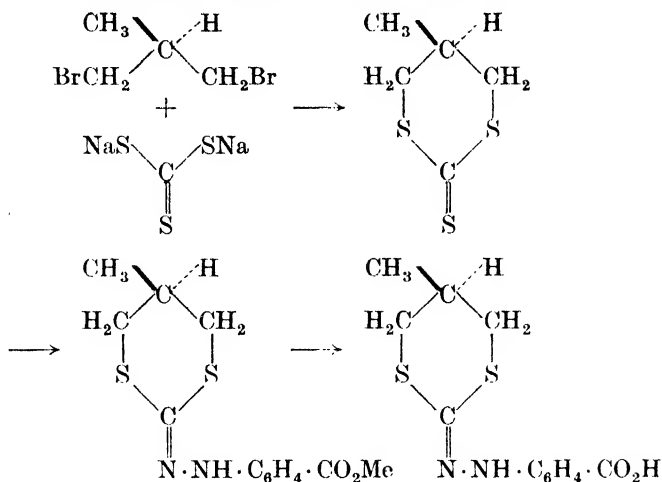
It will be seen that this compound is of the same stereochemical type as the first, the differences being that there are two sulphur atoms instead of methylene groups in the ring, so that the above isomeric change is impossible; the compound is a phenylhydrazone and not an oxime, but this fact is immaterial since the two classes, having the group $>C=N—$ in common, must have the same space-arrangement. This compound was resolved with great ease by crystallization of its quinine salt. Both the acid and its sodium salt showed great optical stability and only racemized very slowly. Mills discusses in detail the possibility of the compound resolved having a structure different from that given above and shows that this is extremely unlikely. This brilliant investigation can be taken as conclusive evidence that Hantzsch and Werner were correct in their fundamental assumptions.

The third argument is that, if geometrical isomerism exists in the oximes, we should also expect to find it in other compounds containing the grouping $>C=N—$. Such cases have been known since 1890[1] in the hydrazones and their derivatives. Some of these are true hydrazones, containing the group $>C:N \cdot NH_2$, while others are phenylhydrazones with $>C:N \cdot NH\phi$, but the possibility that the two isomers differ structurally in the position of a hydrogen atom ($>C=N \cdot NH_2$ and $>CH—N=NH$) is excluded by the fact that B. Overton[2] found examples of isomeric diphenylhydrazones ($>C:N \cdot N\phi_2$) in which there is no potentially mobile hydrogen atom, and similar cases were established later by M. Busch, L. Wesely, and O. Küspert.[3] The isomerism of the hydrazones is exactly parallel to that of the oximes in that a symmetrical ketone, $R \cdot CO \cdot R$, never gives two isomeric hydrazones.

Finally, the following extension of one of the original arguments of Hantzsch and Werner will be mentioned. They pointed out that a

[1] H. C. Fehrlin, *Ber.* 1890, **23**, 1574; A. Krause, ibid. 3617.
[2] Ibid. 1893, **26**, 18.   [3] Ibid. 1931, **64**, 1589.

symmetrical α-diketone, such as benzil, $\phi \cdot CO \cdot CO \cdot \phi$, should give rise to two monoximes and three dioximes. If a substituent is introduced into one of the phenyl groups, then there should be four monoximes and four dioximes, two of the latter having the *amphi* configuration.

$$
\begin{array}{cccc}
\text{Ar·CO—C·Ar'} & \text{Ar·CO—C·Ar'} & \text{Ar·C—CO·Ar'} & \text{Ar·C—CO·Ar'} \\
\| & \| & \| & \| \\
\text{NOH} & \text{HON} & \text{HON} & \text{NOH}
\end{array}
$$

Monoximes

$$
\begin{array}{cccc}
\text{Ar·C—C·Ar'} & \text{Ar·C \quad C·Ar'} & \text{Ar·C—C·Ar'} & \text{Ar·C—C·Ar'} \\
\| \quad \| & \| \quad \| & \| \quad \| & \| \quad \| \\
\text{HON \ NOH} & \text{NOH HON} & \text{NOH NOH} & \text{HON HON}
\end{array}
$$
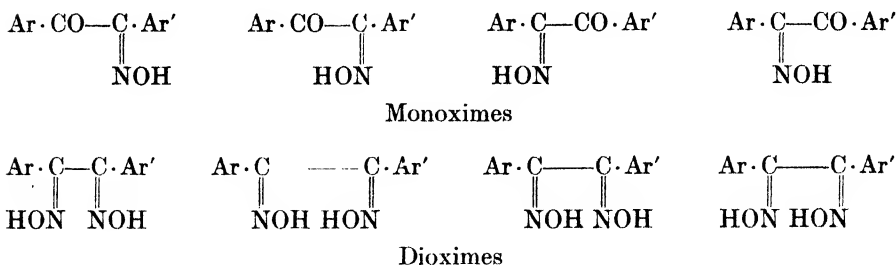
Dioximes

Four substituted benzils have been investigated, the substituents being *p*-methoxyl, and *o*-, *m*-, and *p*-methyl, and in each the expected number of monoximes and dioximes has been obtained.[1]

The properties and relationship of isomeric oximes are best illustrated by a short description of typical cases. If benzaldehyde is allowed to react with hydroxylamine in the presence of excess of aqueous sodium hydroxide, α-benzaldoxime is formed and remains in solution as its sodium salt: it can be precipitated by carbon dioxide as a colourless oil. The oxime occurs in two polymorphous forms, one melting at 5° and the stable form at 35°, but in the liquid state it is supercooled very readily and it is often very difficult to cause a sample to solidify. On acetylation an acetyl derivative can be obtained (m.p. 14–16°), which regenerates the oxime on treatment with alkalis. If dry hydrogen chloride is passed into an ethereal solution of the oxime at a temperature below 0°, a crystalline hydrochloride is obtained (m.p. 103–105°), but this hydrochloride is somewhat unstable, and on recrystallization is converted into the hydrochloride of β-benzaldoxime. This same product is obtained by the action of hydrogen chloride on the α-oxime without cooling. The free β-oxime can be obtained by the action of sodium carbonate on the hydrochloride; the β-oxime is rapidly converted into the α-oxime on heating or in the presence of traces of acids. It forms colourless crystals melting at 126°; its acetyl derivative (m.p. 55–56°) on treatment with sodium or potassium carbonate is converted by loss of acetic acid into benzonitrile.

The behaviour described above is typical of the isomeric aromatic aldoximes. The most marked difference between the isomers is the behaviour of the acetyl derivatives towards alkali carbonate; the oxime

[1] J. Meisenheimer, H. Lange, and W. Lamparter, *Annalen*, 1925, **444**, 94; J. Meisenheimer, O. Beisswenger, H. O. Kauffmann, U. v. Kummer, and J. Link, ibid. 1929, **468**, 202; the monoxime of *p*-methylbenzil which Meisenheimer could not obtain has been prepared by T. W. J. Taylor, N. J. Mawby, and Miss G. M. Price, *J.C.S.* 1931, 2019; G. Ponzio raises objections to this argument, *Ber.* 1928, **61**, 1316, but see J. Meisenheimer and W. Theilacker, *Annalen*, 1929, **469**, 128.

which can be regenerated from its acetyl derivative is generally called the α-oxime, and the other the β-oxime. β-Oximes can usually be transformed into the isomeric α-oximes with great ease; the reverse change can be effected via the hydrochlorides, of which the β-hydrochloride is more stable than the α-form, by the action of sulphuric acid and sometimes by the action of ultra-violet light;[1] this latter method is a clear demonstration of the higher energy content of the β-form. The β-aldoximes usually form metallic derivatives with metals such as copper and iron; the α-oximes seem, in general, to form no such derivatives, but by the action of the metallic salt[2] are converted into the metallic derivative of the β-oxime.[3]

The behaviour of the isomeric aromatic ketoximes is rather different from that of the aldoximes. Usually both isomers are formed by direct oximation of the ketone and the separation of the two is effected by fractional crystallization or precipitation, or, as in the case of the oximes of p-nitrobenzophenone, by taking advantage of the difference in solubility of the sodium salts in aqueous caustic soda. One form is more stable than the other, and the less stable form can be converted into the stable by continued heating of its solution in a solvent such as alcohol. Ultra-violet light effects the reverse change in some cases, the stable form being partly converted into the less stable.[4] When subjected to agents which bring about the Beckmann transformation, the stable form usually gives only one product, but the less stable oxime very often gives a mixture of two, one arising from its own transformation and one from that of the isomeric stable oxime into which it has been partially converted during the reaction.

Benzil, $\phi \cdot CO \cdot CO \cdot \phi$, gives two isomeric monoximes which have been the subject of much investigation. If the ketone is allowed to react with hydroxylamine at low temperatures, the product is almost entirely the α-oxime, melting-point 140°.[5] If the reaction is carried out at higher temperatures, or if the α-oxime is kept in the molten state, or heated in alcoholic solution, the β-oxime (m.p. 114°) is obtained. The β-oxime is the more stable of the two. The two oximes behave very differently in the formation of metallic derivatives.

On treatment with phosphorus pentachloride, great care being taken to exclude all moisture, the α-oxime is converted into N-benzoyl-benz-iminochloride,[6] while at the same time small quantities of the benzoyl derivative of the β-oxime are formed. The iminochloride is easily hydrolysed to benzoic acid and ammonia:

(α) $\phi \cdot CO \cdot C(:NOH) \cdot \phi \longrightarrow \phi \cdot CCl:N \cdot CO\phi \longrightarrow 2\phi \cdot CO_2H + NH_3 + HCl.$
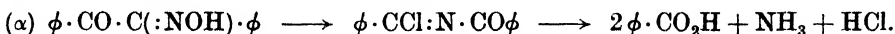
[1] O. L. Brady and G. P. McHugh, *J.C.S.* 1924, **125**, 547.

[2] e.g. cuprous chloride, W. J. Comstock, *Amer. Chem. J.* 1878, **19**, 488.

[3] Cf. W. Hieber and F. Leutert, *Ber.* 1927, **60**, 2306.

[4] R. Stoermer, ibid. 1911, **44**, 667.

[5] K. v. Auwers and M. Siegfeld, ibid. 1893, **26**, 792.

[6] E. Beckmann and K. Sandel, *Annalen*, 1897, **296**, 280.

The β-oxime gives as the main product the anilide of benzoylformic acid, while at the same time some benzoyl chloride and aniline are also formed:

$$(\beta) \quad \phi \cdot CO \cdot C(:NOH) \cdot \phi \longrightarrow \phi \cdot CO \cdot CO \cdot NH\phi.$$
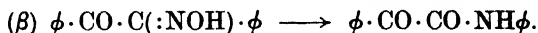
It will be seen that the Beckmann transformation has taken the same course as with the simpler ketoximes; in one case the benzoyl group has migrated to the nitrogen atom, while in the β-oxime the other group, a phenyl radical, has migrated.

If the isomerism of an oxime is geometrical, it should be possible to assign configurations to the two isomers, e.g. to discover whether α-benzaldoxime is (IV) and the β-oxime (V), or vice versa.

$$
\text{IV.} \quad
\begin{array}{c}
\phi \cdot CH \\
\parallel \\
NOH
\end{array}
\qquad
\text{V.} \quad
\begin{array}{c}
\phi \cdot CH \\
\parallel \\
HON
\end{array}
$$

When Hantzsch and Werner put forward their explanation of oxime isomerism, they also suggested general methods for the determination of configuration, one for the aldoximes, and one for the ketoximes. For this purpose it is obviously useless to pay attention to the properties and reactions in which the isomers resemble one another: attention must be focused upon the points in which they differ. Now Hantzsch and Werner pointed out that in the case of the aldoximes one reaction in which there is a marked difference is in the behaviour of the two isomeric acetyl derivatives towards aqueous sodium carbonate; one is hydrolysed to the oxime, while the other loses acetic acid to give a nitrile. If it is assumed that the latter loses acetic acid easily because the hydrogen atom is spatially close to the acetyl group, or, in other words, if it is assumed that the loss of acetic acid involves groups lying on the same side of the double bond, then the configurations of two isomeric aldoximes follow.

$$
\begin{array}{c}
R \cdot CH \\
\parallel \\
CH_3 \cdot CO \cdot ON
\end{array}
\longrightarrow
\begin{array}{c}
R \cdot CH \\
\parallel \\
HON
\end{array}
\qquad
\begin{array}{c}
R \cdot CH \\
\parallel \\
NO \cdot CO \cdot CH_3
\end{array}
\longrightarrow
\begin{array}{c}
R \cdot C \\
\vertiii{\ } \\
N
\end{array}
+ CH_3 \cdot CO_2H
$$
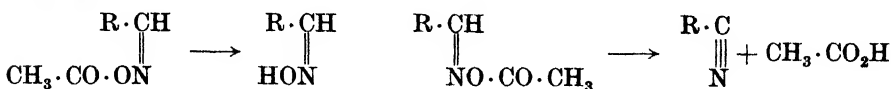
On the basis of this assumption they allotted configurations to the aldoximes, calling those which on their view had the hydrogen atom attached to carbon and the hydroxyl group attached to nitrogen on the same side of the double bond *syn*-aldoximes and those of the other configuration *anti*-aldoximes. Thus α-benzaldoxime was an *anti*-oxime, and β-benzaldoxime a *syn*-oxime.

The ketoximes do not, in general, undergo any reaction of this type, and hence another criterion must be found. When two isomeric ketoximes undergo the Beckmann transformation, the products are different; of two oximes of constitution $R \cdot C(:NOH) \cdot R'$, one gives as its main product the amide $R \cdot CO \cdot NHR'$, while the other gives the isomeric amide $R'CO \cdot NHR$. If the assumption is made that the groups which exchange places are those in the *syn* position to one another, then the configurations of the ketoximes are known.

$$R \cdot \underset{\parallel}{C} \cdot R' \longrightarrow R \cdot \underset{\parallel}{C} \cdot OH \longrightarrow R \cdot \underset{\mid}{C} : O$$
$$NOH \qquad\qquad NR' \qquad\qquad NHR'$$

$$R \cdot \underset{\parallel}{C} \cdot R' \longrightarrow HO \cdot \underset{\parallel}{C} \cdot R' \longrightarrow O : \underset{\mid}{C} \cdot R'$$
$$HON \qquad\qquad RN \qquad\qquad NHR$$
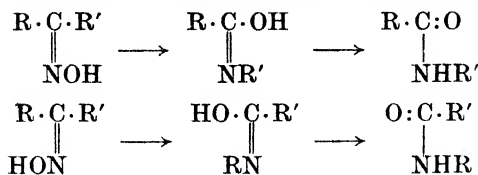
On this basis the configurations of the benzilmonoximes will be:

$$\phi \cdot \underset{\parallel}{C} \text{———} \underset{\parallel}{C} \cdot \phi \qquad\qquad \phi \cdot \underset{\parallel}{C} \text{—} \underset{\parallel}{C} \cdot \phi$$
$$O \ \ HON \qquad\qquad\qquad O \ \ NOH$$

α-Benzilmonoxime　　　β-Benzilmonoxime
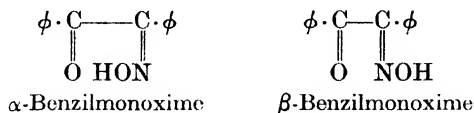
The assumptions made in these arguments were in agreement with what was believed at the time concerning the analogous reactions involving groups attached to the system $>C=C<$. The assumptions have proved to be erroneous, but it should be pointed out that the two reactions chosen by Hantzsch and Werner, one for the aldoximes and one for the ketoximes, still remain the crucial test for determining configurations of oximes. No other general reactions which distinguish so clearly between two isomers have been found, and subsequent work has been largely concerned with establishing the truth or falsity of the two assumptions.

In passing it is worth noticing that there is one class of dioximes whose configuration follows from the products of the Beckmann transformation irrespective of whether the Hantzsch-Werner assumption or its converse is true. An example is γ-benzildioxime, which is converted by phosphorus pentachloride into N-phenyl-N′-benzoylurea. It will be seen that whether a *syn* or *anti* mechanism is assumed, the *amphi* configuration (i.e. that shown below) follows.

syn assumption

$$\phi \cdot \underset{\parallel}{C} \text{———} \underset{\parallel}{C} \cdot OH \longrightarrow \phi \cdot \underset{\parallel}{C} OH \longrightarrow$$
$$NOH \ \ N\phi \qquad\qquad N\text{—}CO$$
$$\qquad\qquad\qquad\qquad\qquad | $$
$$\qquad\qquad\qquad\qquad\qquad NH\phi$$

$$\phi \cdot \underset{\parallel}{C} \text{———} \underset{\parallel}{C} \cdot \phi$$
$$NOH \ \ NOH$$

anti assumption

$$HO\underset{\parallel}{C} \text{—} \underset{\parallel}{C} \cdot \phi \longrightarrow HO\underset{\parallel}{C} \cdot \phi \longrightarrow$$
$$N\phi \ \ NOH \qquad\qquad OC\text{—}N$$
$$\qquad\qquad\qquad\qquad\qquad | $$
$$\qquad\qquad\qquad\qquad\qquad NH\phi$$

$$\underset{\diagdown}{\overset{\diagup NH \cdot CO\phi}{CO}}$$
$$\qquad NH\phi$$
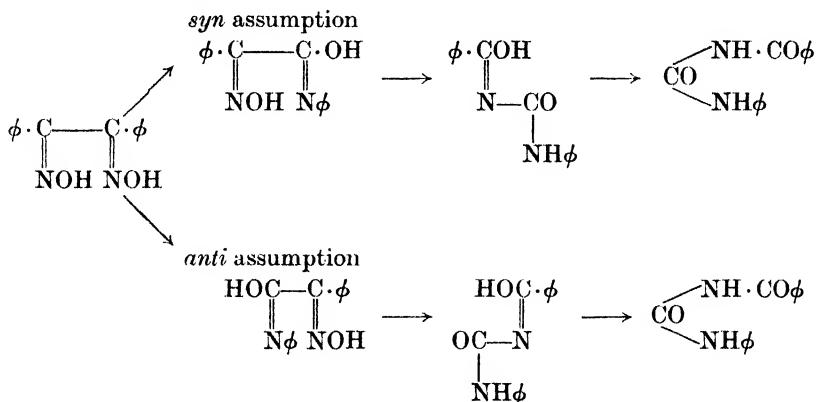
The case of the ketoximes will be discussed first. Doubts as to the validity of the Hantzsch-Werner assumption were expressed quite early,[1] and a few difficulties arising from the configurations deduced from it were known to exist. It was not, however, until 1921 that the matter

[1] Cf. P. Pfeiffer, *Z. phys. Chem.* 1904, **48**, 62.

came to a head. In this year Meisenheimer published his famous paper on the product obtained by the oxidation of triphenylisoxazole.[1] It is clear that the most satisfactory way of settling the question as to which groups are involved in the Beckmann rearrangement would be to find some unambiguous argument independent of that rearrangement for establishing the configuration of an oxime, and then to investigate the course of the rearrangement and deduce which groups must have been involved. The trouble is obviously that it is difficult to find an argument which itself is free from assumptions of one kind or another.

Meisenheimer was investigating the oxidation products of triphenylisoxazole and found that, though the compound is stable towards permanganate, it is attacked by chromic acid in hot acetic acid solution and by ozone in the cold. The main product of the reaction in either case is the benzoyl derivative of β-benzilmonoxime. Now the action of ozone on doubly bound carbon atoms results in fission at the double bond, the atoms at the point of division being oxidized to carbonyl groups. If it is assumed that in the case under discussion the ring has opened in this simple manner, the configuration of β-benzilmonoxime must follow from these observations and must be that shown below:

$$\phi \cdot \underset{\underset{\displaystyle N}{\|}}{C}\!\!-\!\!\underset{\underset{\displaystyle C\cdot\phi}{\|}}{C}\cdot\phi \qquad \longrightarrow \qquad \phi\cdot\underset{\underset{\displaystyle N}{\|}}{C}\!\!-\!\!CO\cdot\phi$$
$$\underset{\displaystyle O}{\diagdown\!\!\!\diagup} \qquad\qquad \diagdown O\cdot CO\cdot\phi$$
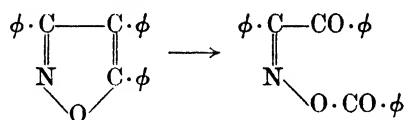
But it was already known that the Beckmann rearrangement of this oxime gives the anilide of benzoylformic acid, and this product can only be formed if that rearrangement has involved the groups in the *anti* position to one another.

$$\phi\cdot\underset{\underset{\displaystyle NOH}{\|}}{C}\!\!-\!\!CO\cdot\phi \qquad\longrightarrow\qquad HO\underset{\underset{\displaystyle N\phi}{\|}}{C}\!\!-\!\!CO\cdot\phi \qquad\longrightarrow\qquad \phi HN\cdot CO\cdot CO\cdot\phi$$
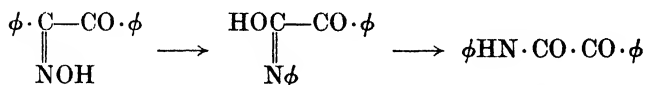
This argument involves the assumption that the opening of the isoxazole ring has not been accompanied by stereochemical reversal of the configuration about the $\diagup\!\!\!>\!\!C\!=\!N\!\!-$ group. Since the argument leads to the opposite conclusion to that reached by the original assumption of Hantzsch and Werner, it is a matter of deciding which of the two assumptions is the more probable, and there is no doubt that that of Meisenheimer must be preferred, especially since the ring-opening is a reaction that can be carried out at room temperature where stereochemical inversion is not very probable.

These results with triphenylisoxazole do not constitute an exceptional and abnormal case. Exactly similar ones were obtained with substituted compounds,[2] and E. P. Kohler[3] has shown that diphenylisoxazole carboxylic acid on oxidation loses carbon dioxide and gives β-benzilmonoxime itself.

[1] *Ber.* 1921, **54**, 3206.   [2] J. Meisenheimer and H. Lange, ibid. 1924, **57**, 282.
[3] *J. Amer. C. S.* 1924, **46**, 173.

$$\phi\cdot C\!\!-\!\!-\!\!C\cdot\phi \longrightarrow \phi\cdot C\!\!-\!\!-\!\!C\cdot\phi$$
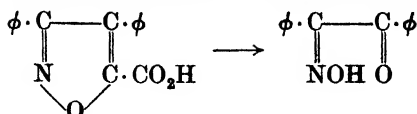
Meisenheimer advanced another series of arguments showing that the Beckmann rearrangement involved the groups in the *trans* position to one another. These were based, not on the phenomena of ring-opening, but on the converse assumption that ring-closure takes place most easily if the atoms eliminated in the closure are spatially close together in the original molecule. An example of this argument is the behaviour of the oximes of 2-bromo-5-nitro-acetophenone: of these the β-oxime (m.p. 132°) passes with great ease into 2-methyl-4-nitro-indoxazene, while the α-oxime does not. On the assumption made, the configurations must be:
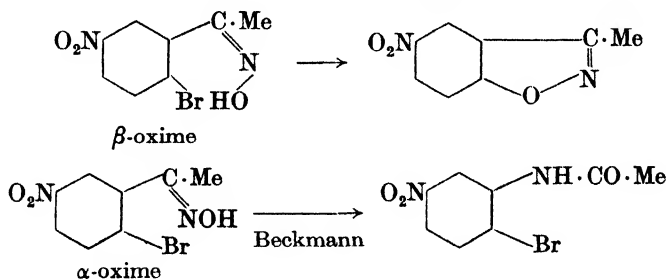
β-oxime

α-oxime

Now the Beckmann rearrangement of the α-oxime gives 2-bromo-5-nitro-acetanilide, but the β-oxime, unfortunately, refuses to undergo the rearrangement. If the assumption is accepted, these facts support the *trans* view of the rearrangement.[1]

There seems little doubt that the assumption made in this argument is correct, but unfortunately in every case where the argument might be applied, some difficulty is reached: only one isomer can be obtained, or one refuses to undergo the Beckmann rearrangement. A much more powerful argument and, at the same time, one of the most ingenious investigations in the whole of stereochemistry is the work of J. Meisenheimer, W. Theilacker, and O. Beisswenger.[2] It is known that certain compounds, notably derivatives of diphenyl with substituents in the ortho positions, exist in enantiomorphous forms because free rotation about the single bond uniting the two nuclei is rendered impossible by the purely steric interference of the substituents. Any substituent of sufficient volume is capable of inhibiting the rotation and it is known that, for 1-substituted naphthalene compounds, the carbon atom in the 8 position is an ortho-substituent; thus 2,2'-diamino-1,1'-dinaphthyl (VI) has been resolved.[3] If we now consider two isomeric oximes such as those of 1-acetyl-2-hydroxynaphthoic acid (VII and VIII), the possibility presents

[1] J. Meisenheimer, P. Zimmermann, and U. von Kummer, *Annalen*, 1925, **446**, 205.   [2] Ibid. 1932, **495**, 249.

[3] R. Kuhn and P. Goldfinger, ibid. 1929, **470**, 183.

itself that one (VIII) will display atropic enantiomorphism of the kind described and might be resolved, because the hydroxyl group of the oxime grouping prevents free rotation about the bond in the 1-position. In the isomeric oxime (VII) the hydroxyl group will be on the other side of the $>C=N-$ group, interference will not take place and resolution into optical antimers should be impossible.

VI.   VII.

VIII.
resolvable
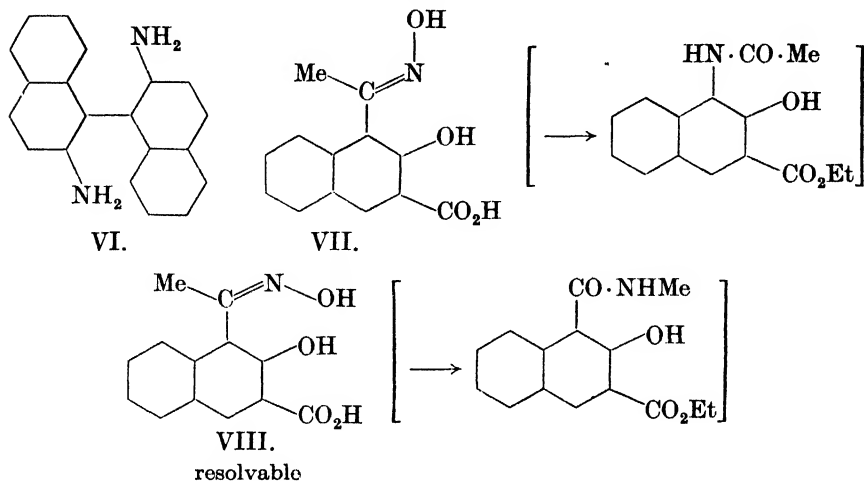
Meisenheimer succeeded in showing that one of these oximes can be resolved and the other cannot, and this work is a brilliant demonstration of the truth of the theory of oxime isomerism and at the same time conclusive evidence as to the configurations of these oximes. The oximes in the form of their ethyl esters undergo the Beckmann rearrangement, and since the non-resolvable oxime gives 1-acetylamino-2-hydroxynaphthoic ester and the resolvable one the methylamide of the half ester of 2-hydroxynaphthalene-1,3-dicarboxylic acid, as shown, the evidence is complete that the *trans* groups have rearranged.

These arguments all support the same conclusion, but it would clearly be of importance if evidence could be found from the simple physical properties of a pair of isomeric oximes. The interpretation of the majority of such properties in terms of the configurations usually involves assumptions of doubtful validity, and some of the arguments based on dissociation constants, melting-points, &c., which have been advanced can be shown to give inconsistent results.[1] The reason for this is very largely that such properties are not those of an isolated molecule but of an assembly of molecules. The importance of the electric moment is that it refers to an isolated molecule, and in some cases can give direct evidence of the configuration. Thus J. Errera[2] found that of the two geometrically isomeric dichlorethylenes, one has an electric moment of 1·9 D while that of the other is zero. It is clear that the molecule of the latter must be such

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[1] J. Meisenheimer and W. Theilacker, *Annalen*, 1929, **469**, 128.

[2] *C.r.* 1926, **182**, 1623; *Phys. Z.* 1926, **27**, 754.

that the constituent moments of the various linkages cancel out, i.e. that it must be the *trans* compound.

$$\mu = 1\cdot9\ D \qquad\qquad \mu = 0$$
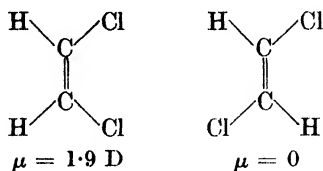
The moments of the oximes themselves cannot be obtained since they are largely associated in solution:[1] they appear to have very small moments which are those of the association complexes. Their N-ethers, however, do not associate and contain a semi-polar double bond N→O, which by analogy with the nitro group will have a large electric moment, the positive pole of which lies towards the nitrogen atom. The two N-methyl ethers of *p*-nitrobenzophenone oxime can then be written as shown, with the symbol ⊢⟶ indicating the principal contributions to the total moment.

$$\mu = 1\cdot09\ D \qquad\qquad \mu = 6\cdot6\ D$$
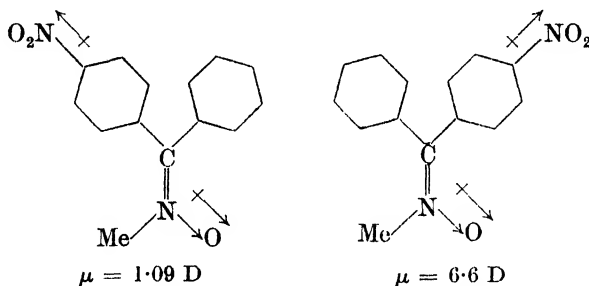
L. E. Sutton and T. W. J. Taylor[2] prepared the two ethers and measured their moments, which were very different, 1·09 D and 6·6 D. It is clear that these results prove the configurations of the two ethers. The oximes can be converted into the ethers without any stereochemical inversion and hence the configuration of the two oximes is known. The oximes undergo the Beckmann rearrangement each to give a single product. The oxime related to the N-ether of small moment gives benzo-*p*-nitranilide, and the other *p*-nitrobenzanilide, and hence it is clear that the groups which rearrange are in the *trans* position in the oxime.

$$O_2N\cdot C_6H_4\cdot \underset{\substack{\| \\ NOH}}{C}\cdot\phi \longrightarrow O:\underset{\substack{| \\ NH\cdot C_6H_4\cdot NO_2}}{C}\cdot\phi \qquad \phi\cdot \underset{\substack{\| \\ NOH}}{C}\cdot C_6H_4\cdot NO_2 \longrightarrow O:\underset{\substack{| \\ NH\phi}}{C}\cdot C_6H_4\cdot NO_2$$
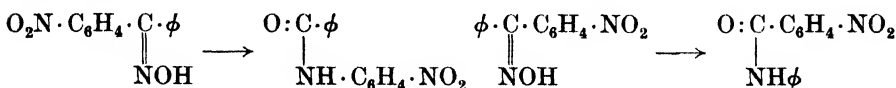
The agreement between these arguments, based on experimental material of extremely different nature, is very striking and is conclusive evidence that the original assumption of Hantzsch and Werner was in error and that configurations can be accurately allotted to ketoximes by

[1] O. Hassel and E. Naeshagen, *Z. phys. Chem.* 1929, B, **4**, 217.
[2] *J.C.S.* 1931, 2190.

assuming that the Beckmann rearrangement involves groups in the *trans* position to one another.

The case of the aldoximes remains for discussion. The configurations allotted to these by Hantzsch and Werner were based on the assumption that if an acetyl-aldoxime loses acetic acid when warmed with aqueous sodium carbonate, the acetyl group and the hydrogen atom are on the same side of the double bond. As with the ketoximes, the truth of such an assumption can only be tested by establishing the configurations by some independent method. Two important methods have been used and they both point to the same conclusion, that the loss of acetic acid involves the *trans* and not the *cis* groups, and it is upon this conclusion that the configuration of the aldoximes is based.

$$\phi \cdot \underset{\text{NOH}}{\overset{\text{CH}}{\|}} \qquad\qquad \phi \cdot \underset{\text{HON}}{\overset{\text{CH}}{\|}}$$

α-Benzaldoxime   β-Benzaldoxime
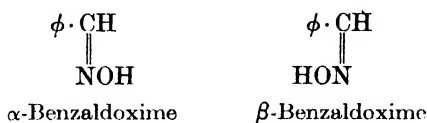
The first of these methods is an argument from ring-closure similar to that for ketoximes given above. O. L. Brady and G. Bishop[1] prepared the isomeric oximes of 2-chloro-5-nitrobenzaldehyde and found that with alkalis the β-oxime lost hydrogen chloride very readily while the α-oxime did not. The product from the β-oxime is nitrosalicylic nitrile which is formed from the intermediate ring compound, the indoxazene. Hence the β-oxime must have the configuration shown and since its acetyl derivative loses acetic acid and is not hydrolysed to the oxime, the converse of Hantzsch's assumption must be true.
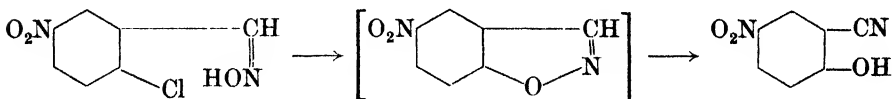
The argument from electrical moments cannot be applied as in the ketoxime case, because the simpler aldoximes in general never give two isomeric N-ethers; the reason for this is unknown.[2] However, aldoximes often give two isomeric O-ethers, and T. W. J. Taylor and L. E. Sutton[3] have been able to deduce the configurations of two isomeric aldoximes by comparison with the two closely related ketoximes, whose configurations can be taken as known from the arguments given above. Taking the configurations of the *p*-nitrobenzophenone oximes as known, one can measure the moments of their O-methyl ethers, and compare them with the values of the moments of the O-methyl ethers of the *p*-nitrobenzaldoximes.

[1] *J.C.S.* 1925, **127**, 1357.

[2] The only isomeric N-ethers of aldoximes known are those of 3-amino-2,6-dichlorobenzaldoxime, J. Meisenheimer, W. Theilacker, and O. Beisswenger, *Annalen*, 1932, **495**, 253.

[3] *J.C.S.* 1933, 63.

$$O_2N\!\!\left\langle\bigcirc\right\rangle\!\!-\!\overset{\displaystyle C\cdot\phi}{\underset{MeON}{\|}}\quad \mu = 3\cdot75\,D \qquad O_2N\!\!\left\langle\bigcirc\right\rangle\!\!-\!\overset{\displaystyle C\cdot H}{\underset{MeON}{\|}}\quad \mu = 3\cdot39_5\,D$$

β-O-Methyl ether

$$O_2N\!\!\left\langle\bigcirc\right\rangle\!\!-\!\overset{\displaystyle C\cdot\phi}{\underset{NOMe}{\|}}\quad = 4\cdot26 \qquad O_2N\!\!\left\langle\bigcirc\right\rangle\!\!-\!\overset{\displaystyle C\cdot H}{\underset{NOMe}{\|}}\quad = 3\cdot88_5$$
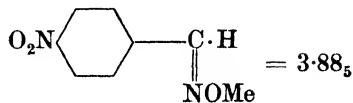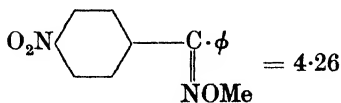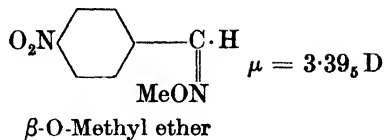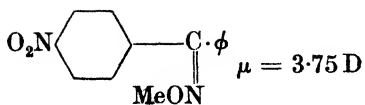
Difference = 0·51 α-O-Methyl ether   Difference 0·49

Since the differences between two isomeric ethers arise solely from the difference in configuration and are identical in the two cases, it can be concluded that the aldoxime ether and ketoxime ether with the smaller moments have the same configuration. That of the ketoxime is known and hence that of the aldoxime follows. The result agrees with that of the ring-closure experiments, and thus it seems that the configurations of the aldoximes is known with certainty and that the benzaldoximes, for example, have those shown above.

Only a restricted number of oximes can be obtained in the two geometrically isomeric forms. Among ketoximes isomerism has been observed in the unsymmetrically substituted benzophenone oximes and those of the type of the oximes of benzil, and in addition a few other cases, such as camphor quinone monoxime and the oxime of mesityl oxide. The aldoximes known in two forms are principally the substituted benzaldoximes, but other examples are known, such as the oximes of cinnamaldehyde, $\phi CH\!:\!CH\cdot CHO$, and furfural. The configuration of an oxime which exists in only one form can be established by the general methods described above. The ketoximes of this type fall into two classes; in the first the oxime gives a mixture of two amides as the result of the Beckmann transformation, and thus behaves in solution as if it were a mixture of the two possible configurations, while the second class gives only one amide and seems to exist in solution in only one configuration. These facts indicate that the reasons for the existence of an oxime in only one form are twofold. In the first class there is an extremely ready interconversion of the two forms, so that in solution both exist; when, however, the oxime crystallizes from solution, the less soluble form separates, and this upsets the equilibrium between the two in solution; hence more of the less soluble form is produced and this crystallizes out until eventually all the oxime is obtained in this form. With the oximes of the second class there must be a great difference in the energy content of the two possible configurations, so that the change into the more stable form is irreversible and only one form can exist. The difference in energy content arises from the interactions between the various parts of the molecule, and, to judge by the facts which have been recorded, these interactions are of two kinds, electrical and purely steric. Acetophenone oxime exists as one substance which gives nothing but acetanilide on the Beckmann transformation. Its configuration

is thus (I). The two forms of the oxime of ω-bromoacetophenone are, however, known (II), and hence it seems that the introduction of the bromine atom into the side chain has altered the interactions between the parts of the molecule.

$$\text{I.} \quad \begin{array}{c} \phi \cdot \text{C} \cdot \text{CH}_3 \\ \| \\ \text{NOH} \end{array} \qquad \text{II.} \quad \begin{array}{c} \phi \cdot \text{C} \cdot \text{CH}_2\text{Br} \\ \| \\ \text{NOH} \end{array} \qquad \begin{array}{c} \phi \cdot \text{C} \cdot \text{CH}_2\text{Br} \\ \| \\ \text{HON} \end{array}$$
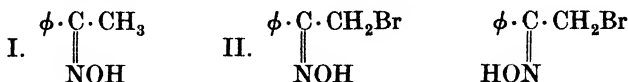
On the other hand, methyl-n-propyl-ketoxime (III) gives two amides as products of the Beckmann transformation, behaving as though both forms were present in solution, while methyl isopropyl ketoxime (IV) gives only one amide and behaves as a single substance. It is unlikely that the electrical fields of the propyl and isopropyl groups are widely different, but the space they occupy in the vicinity of the oxime hydroxyl group must differ. Consequently it seems that the oxime with the isopropyl group behaves as if it is a pure substance because one form cannot exist owing to purely steric interactions between the hydroxyl and isopropyl groups. This view is confirmed by the fact that the amide obtained from the one known oxime by the Beckmann transformation shows that these two groups lie on opposite sides of the double bond.

$$\text{III.} \quad \begin{array}{c} \text{CH}_3 \cdot \text{C} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3 \\ \| \\ \text{NOH} \end{array}$$

$$\text{IV.} \quad \begin{array}{c} \text{CH}_3 \cdot \text{C} \cdot \text{CH} \\ \| \quad \diagdown \\ \text{HON} \quad \text{CH}_3 \end{array}^{\diagup \text{CH}_3} \longrightarrow \text{CH}_3 \cdot \text{CO} \cdot \text{NH}-\text{CH} \diagdown_{\text{CH}_3}^{\diagup \text{CH}_3}$$
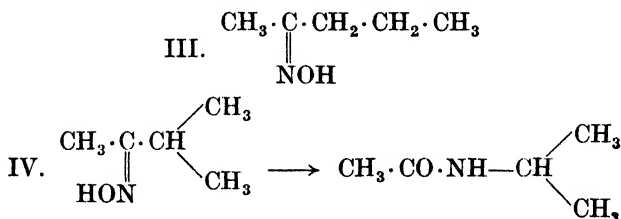
Of the many other points that arise from oxime isomerism, only a few can be mentioned.[1] The mechanism of the Beckmann rearrangement has been the subject of great controversy, and a variety of mechanisms have been proposed, many of which have since been shown by experiment to be untrue.[2] The important discoveries in this field were by M. Kuhara,[3] who found that the benzenesulphonyl ester of benzophenone oxime could be obtained as a crystalline solid and that at 62° it isomerized spontaneously and without the need for any catalyst into a yellow oil which is very easily hydrolysed to benzanilide and benzene sulphonic acid.

$$\begin{array}{c} \phi \cdot \text{C} \cdot \phi \\ \| \\ \text{N} \cdot \text{O} \cdot \text{SO}_2 \cdot \phi \end{array} \longrightarrow \begin{array}{c} \phi \cdot \text{SO}_2 \cdot \text{O} \cdot \text{C} \cdot \phi \\ \| \\ \text{N}\phi \end{array} \longrightarrow \begin{array}{c} \text{O} : \text{C} \cdot \phi \\ | \\ \phi \cdot \text{SO}_2 \cdot \text{N} \end{array}$$
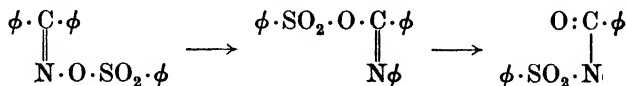
A. W. Chapman[4] has shown that the picryl ethers of oximes also undergo a spontaneous Beckmann rearrangement on heating, in which no catalyst

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[1] A detailed account of the whole subject will be found in the article by J. Meisenheimer and W. Theilacker, *Stereochemie*, ed. Freudenberg, Leipzig, 1933.

[2] A detailed discussion will be found in the article by A. H. Blatt, *Chem. Rev.* 1933, **12**, 240.   [3] *Mem. Coll. Sci. Kyoto Imp. Univ.* 1914, **1**, 105.

[4] *J.C.S.* 1933, 806; 1934, 1550.

is needed and considerable energy is evolved. The first product of these reactions is probably an imino-ester, $R' \cdot C(OAc):NH$, which is known to change ir to the isomeric N-acyl compound, $R' \cdot CO \cdot NHAc$, with great ease. In view of these results there seems little doubt that the Beckmann rearrangement is a simple intramolecular change which takes place in the acyl derivatives of the oximes, and the more readily the more acidic the acyl group. The function of the various reagents used to bring about the change with the oximes themselves, such as phosphorus pentachloride, is to unite with the oxime to form the acyl derivative capable of rearrangement.[1]

The interconversion of isomeric oximes can be performed in various ways. Of two isomers usually one is less stable than the other and tends to pass into the more stable form on heating or in the presence of catalysts. With the benzilmonoximes, where the α-oxime is the less stable, the rate of change can be measured because only the α-oxime reacts with copper acetate to give an oxime-copper complex and this fact can be applied to the analysis of a mixture of the α- and β-oximes.[2] In alcoholic solution, hydrogen chloride is an effective catalyst, but the rate of change is not proportional to its concentration; at low concentrations the rate is inappreciable, and above a concentration of 2N hydrogen chloride it increases extremely rapidly. More surprisingly, salts such as lithium chloride and tetramethylammonium chloride are more efficient catalysts than hydrogen chloride at the same concentration, and again the rates of stereoisomeric change are not proportional to the concentration of the salt, but increase very rapidly at the higher concentrations. These facts seem to indicate that the actual catalyst is the undissociated molecule (associated ion-pair) of the catalyst, the concentration of which only becomes appreciable in the more concentrated solutions. The catalysis has obviously nothing to do with the hydrogen ion, or with salt formation by the oxime: it would seem that at the close approach of an ion-pair and a molecule of the α-oxime there is an interaction between the field of the former and the $>C=N-$ system, the result of which is to decrease the torsional rigidity of the double bond so that the α-oxime can change easily into the more stable β-oxime.

A curious example of stereoisomeric change in oximes is afforded by the action of certain charcoals. α-Benzilmonoxime is stable for long periods in hot alcoholic solution, but addition of a little animal charcoal converts it quantitatively into the β-oxime in a few minutes. It has been shown[3] that, though this phenomenon is shown by several oximes, it is not shared by their O-methyl ethers. If the charcoal is heated in hydrogen until all oxygen has been removed from its surface, the effect disappears: the catalyst is the active oxygen adsorbed on the surface of the charcoal, and the mechanism of the catalysis is an exchange of oxygen atoms. If an

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[1] See also A. W. Chapman, *J.C.S.* 1934, 1550; 1935, 1223.

[2] T. W. J. Taylor and D. C. V. Roberts, ibid. 1933, 1439.

[3] T. W. J. Taylor and E. M. W. Lavington, ibid. 1934, 980.

active oxygen atom on the charcoal becomes attached to the nitrogen of the oxime group, it can only do so on the opposite side of the double bond to the hydroxyl group already there. The hydrogen atom of the hydroxyl group can migrate to this new oxygen atom and the oxime molecule can then leave the surface in the more stable β-configuration, leaving behind it the original oxygen atom of the oxime group. This explanation accounts for the absence of the phenomenon in the O-ethers, because the migration of a methyl group is a rare phenomenon, unlike that of a hydrogen atom. The function of the charcoal is to bring the oxygen into a sufficiently reactive state to take part in the exchange, just as gaseous hydrogen will not exchange hydrogen atoms with those of heavy water, except in the presence of a metal such as nickel which will adsorb the hydrogen and hold it in a state where it is chemically reactive.

Metallic Derivatives of the Oximes

Certain oximes will form stable complexes with metals, particularly with those of the transitional triads of the Periodic Table and adjacent groups, and are used widely for the detection and estimation of those metals. Thus the reagent used for the estimation of nickel and palladium is dimethylglyoxime, $HON:CMe \cdot CMe:NOH$. Three examples of such oximes will be discussed.

Salicylaldoxime (I) forms complexes with a variety of metals such as manganese, cadmium, nickel, and copper, which are precipitated in aqueous alcoholic solution, but all these complexes are soluble in dilute acetic acid with the exception of that of copper, and hence F. Ephraim[1] introduced the oxime as a qualitative and quantitative reagent for copper. The complex is a pale greenish yellow powder which can be dried without decomposition at 110°: its composition is $Cu(C_7H_6O_2N)_2$, one hydrogen atom of each oxime molecule having been replaced, and it is clearly not a true salt but a complex in which the copper is showing the co-ordination number of four. Its structure has been established by F. Feigl and A. Bondi.[2] They prepared the two methyl ethers of the oxime (II and III) and found that a copper complex is only formed by the oxime ether (III).

I. (benzene ring with CH:NOH and OH substituents)   II. (benzene ring with CH:NOH and OMe substituents)   III. (benzene ring with CH:NOMe and OH substituents)
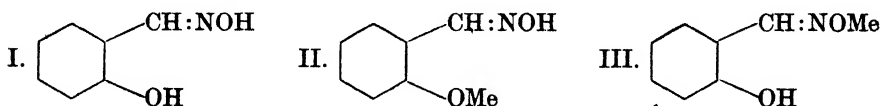
Hence the hydrogen atom of salicylaldoxime which has been replaced in the copper complex is that of the phenolic hydroxyl group. The copper is obviously attached to the oxime groups by co-ordinate links, and these can be formed either by the nitrogen or oxygen atom of that group. If the union is to the nitrogen atom, the complex contains six-membered rings (IV), and hence this formula is more probable than one in which the union

[1] *Ber.* 1930, **63**, 1928; 1931, **64**, 1215.   [2] Ibid. 1931, **64**, 2819.

is to oxygen, when the rings would contain seven atoms. Further, this view

implies a stereochemical configuration for the oxime (of which only one isomer is known), in that the hydroxyl group of the oxime grouping must lie on the same side of the $\diagup$C=N— bond as the hydrogen atom attached to the carbon atom of the aldehyde group; otherwise it would occupy the position attributed to copper in formula (IV) and this structure would be impossible. This configuration of salicylaldoxime so reached agrees with that deduced from other observations on the compound. It is an α-aldoxime, i.e. its acetyl derivative is hydrolysed back to the oxime; in many of its chemical and physical properties it differs markedly from the isomeric m- and p-hydroxy-benzaldoximes, and behaves as though the phenolic properties were suppressed,[1] a fact which can best be explained by a formula such as (V), in which the phenolic hydrogen atom is joined by a hydrogen-bond to nitrogen.

If salicylaldoxime is allowed to react in the cold with an alkaline solution of copper, such as Fehling's solution, or if the above complex is treated with caustic soda, a different complex is formed, of composition $Cu(C_7H_5O_2N)$, which is slightly soluble in alcohol and ether with a green colour, and is converted into Ephraim's complex (IV) in the cold by acetic acid.[2] It is extremely unlikely that the configuration of the oxime has been changed in these simple low-temperature reactions, and thus its structure must be (VI). It should be noted that the oxime group is in the nitrone form as in the cases discussed below. Similar complexes are formed by the oximes of many other o-hydroxy aromatic ketones and aldehydes,[3] but oximes of aliphatic compounds such as methyl-acetonyl-carbinol (VII), and chloral-acetophenone (VIII), in which the hydroxyl and oximino groups are separated by the same number of atoms as the aromatic compounds, form no complexes with copper.[2] The difference probably arises partly from a difference in the acidity of the hydroxyl groups, but mainly from the difference in the space arrangements of the groups and the nature of the carbon structure to which they are attached.

VII. Me·CHOH·CH$_2$·C(:NOH)·Me   VIII. CCl$_3$·CHOH·CH$_2$·C(:NOH)·ϕ.

The second class of complexes which will be discussed is that of the monoximes of α-diketones, i.e. compounds containing the group

[1] O. L. Brady, J.C.S. 1931, 105.   [2] Feigl and Bondi, loc. cit.
[3] F. Ephraim, Ber. 1931, 64, 1210.

$\cdot CO \cdot C(:NOH) \cdot$. This group has been known for many years to give marked colorations with solutions of certain metals: one of the earlier observations was that of Baeyer on the deep blue compound of violuric acid and ferrous iron.[1] In 1903 M. A. Whiteley[2] showed that the stereochemical configuration of the monoxime is of importance in complex formation, and that, of the two benzilmonoximes, only the α-oxime gives a blue complex with ferrous iron. L. Tschugaev[3] found that the same phenomenon is true for other metals, notably cobalt and palladium, and it also holds in the case of copper.[4] In cases other than the benzilmonoximes where two isomers are known, it is only the monoxime of configuration corresponding to α-benzilmonoxime which is able to enter into complex formation. The composition of the complexes varies according to the metal present: those of cobalt are usually R_3Co (R $=$ one molecule of oxime less a hydrogen atom), and are dark red crystalline compounds soluble in benzene but not in water. These compounds are extremely stable and are unaffected by boiling with concentrated hydrochloric acid or aqueous potassium cyanide; they cannot be decomposed except with destruction of the oxime residues. With some monoximes cobaltous complexes, R_2Co, are formed.[5] The ferrous complexes are much less stable and some of them are oxidized by atmospheric oxygen with separation of ferric oxide. These monoximes do not unite with trivalent iron and only exceptionally with nickel. The copper complexes are usually of the composition $R \cdot Cu \cdot OH$ and are easily decomposed by dilute acids; their formation can be applied to the quantitative analysis of mixtures of two isomeric oximes of this class.[6]

In these complexes it is clear that each oxime molecule is united to the metal by two links, one covalent, the hydrogen atom of the oxime group having been replaced, and one co-ordinate. This is confirmed by the fact[7] that α-benzilmonoxime reacts readily with *cis*-hydroxo-aquo-diethylenediamine cobaltic bromide, known to have the structure (IX), to form a complex which remains a divalent cation; the hydroxyl group and water molecule, held by a covalency and a co-ordinate link respectively, are replaced by one oxime residue.

$$\text{IX.} \quad \left[en_2Co \underset{OH_2}{\overset{OH}{\diagdown}} \right]^{++} Br_2 \longrightarrow [en_2Co \cdot C_{14}H_{10}O_2N]^{++} Br_2$$
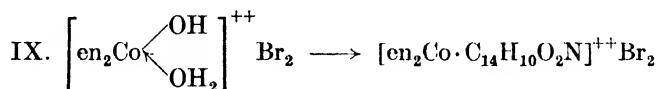
The co-ordinate link must be formed by the electrons of the oxygen atom of the carbonyl group: the only other source would be the nitrogen atom, and this is impossible for stereochemical reasons, as will be seen.

[1] *Annalen*, 1863, **127**, 207.　　　　　　　　　　　　[2] *J.C.S.* **83**, 44.

[3] *Z. anorg. Chem.* 1905, **44**, 146; *J. pr. Chem.* 1907, **76**, 88.

[4] T. W. J. Taylor and E. K. Ewbank, *J.C.S.* 1926, 2818.

[5] G. Ponzio, *Gazz.* 1922, **52**, i. 285.

[6] T. W. J. Taylor and D. C. V. Roberts, *J.C.S.* 1933, 1439.

[7] P. Pfeiffer and J. Richarz, *Ber.* 1928, **61**, 103; P. Pfeiffer and H. Buchholz, *J. pr. Chem.* 1930, **124**, 133.

Thus, since only oximes with the configuration (X) can form complexes, the structure of the complex must be that illustrated in the cobalt complex of α-benzilmonoxime (XI: only one oxime molecule shown in full).[1]

$$
\text{X.} \quad
\begin{array}{cc}
-\text{C}-\text{C}- \\
\parallel \quad \parallel \\
\text{O} \quad \text{NOH}
\end{array}
\qquad
\text{XI.} \quad
\begin{array}{c}
\text{O} \\
\uparrow \\
\searrow\downarrow \quad \nearrow \text{N}=\text{C}\cdot\phi \\
\text{Co} \quad \mid \\
\nearrow \mid \quad \searrow\text{O}=\text{C}\cdot\phi
\end{array}
$$
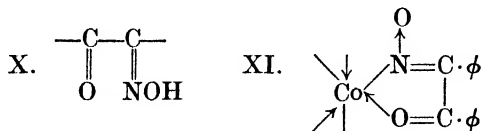
There must be a five-membered ring and the oxime group must be in the nitrone form. The alternative six-ring structure is ruled out because it implies that the oxime is in the β-configuration and it is known that complex formation does not involve the change of the α-configuration to the β-: the copper complex, for example, can be decomposed by dilute acids and the oxime recovered is the α-oxime.

This structure having been established, the difference between the benzilmonoximes in complex formation becomes more comprehensible.[2] The mechanism would appear to be the following, a process which in

$$
\begin{array}{c}
\text{R}\cdot\text{C}-\text{C}\cdot\text{R} \\
\parallel \quad \parallel \\
\text{O} \quad \text{NOH}
\end{array}
+ \text{M}^{+++} \longrightarrow
\begin{array}{c}
\text{R}\cdot\text{C}-\text{C}\cdot\text{R} \\
\parallel \quad \parallel \\
\text{O} \quad \text{NOH} \\
\searrow\swarrow \\
\text{M}^{+++}
\end{array}
\longrightarrow
\begin{array}{c}
\text{R}\cdot\text{C}-\text{CR} \\
\parallel \quad \parallel \\
\text{O} \quad \text{N}\rightarrow\text{O} \\
\searrow\swarrow \\
\text{M}^{++}
\end{array}
+ \text{H}^{+}
$$
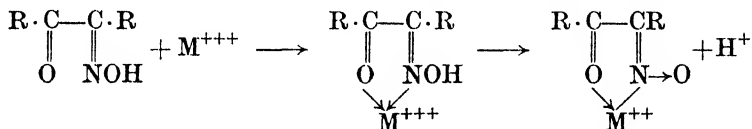
the case of cobalt occurs three times in all to leave an uncharged complex. On this view the β-oxime cannot form a complex because the position of its hydroxyl group prohibits the preliminary stage.

The last example to be discussed is the metallic complexes of the dioximes of α-diketones: these are often described as glyoximes, since they can be regarded as substitution products of the dioxime of glyoxal, OHC·CHO. L. Tschugaev[3] found that compounds of this class form complexes with nickel, palladium, platinum, and copper, and that here again stereochemical configuration is important, since α-benzildioxime gives a series of complexes, but the β-isomer gives none. The composition of these complexes is usually R_2M. Those containing nickel and palladium are formed very readily and are insoluble in water, dilute alkalis, and weak acids. Cobalt does not give an insoluble complex with these oximes, and on this fact depends the use of dimethylglyoxime as an analytical reagent for the separation of nickel and cobalt.[4] The constitution of these complexes has been established by arguments similar to those used above in the case of the oximino-ketones. The configuration of α-benzildioxime is known with certainty from the products of its Beckmann rearrangement, and L. Tschugaev[5] showed that this oxime undergoes no change of con-

[1] Pfeiffer and Richarz, loc. cit.

[2] W. Hieber and F. Leutert, Ber. 1929, 62, 1839.

[3] Z. anorg. Chem. 1905, 46, 144.

[4] For reasons underlying this difference between Ni and Co see E. Thilo, 'Die Valenz der Metalle Fe Co Ni Cu und ihre Verbindungen mit Dioximen', Ahrens' Sammlung, vol. 13, 1932.　　　　　　　　　　　　　　　　[5] Ber. 1908, 41, 1682.

figuration during complex formation because decomposition of its nickel complex with potassium cyanide regenerates the unchanged α-dioxime. Hence the structure of the nickel complex must be that shown in (XII), which was first proposed by Hieber and Leutert.[1]

$$\text{XII.} \quad \begin{array}{c} \text{OH} \quad \text{O} \\ \phi \cdot \text{C}=\text{N} \qquad \text{N}=\text{C} \cdot \phi \\ \quad \quad \text{Ni} \\ \phi \cdot \text{C}=\text{N} \qquad \text{N}=\text{C} \cdot \phi \\ \text{O} \quad \text{HO} \end{array}$$
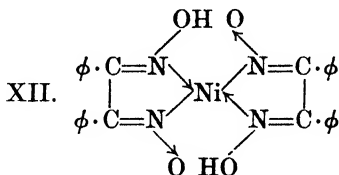
These conclusions deduced from results with α-benzildioxime can be extended to the other oximes of the same type, and the nickel-dimethylglyoxime complex used in analysis can be allotted a formula similar to (XII), methyl groups being substituted for phenyl groups. That the nickel atom in this complex is indeed united by a co-ordinate link to nitrogen has been clearly shown by P. Pfeiffer.[2] He found that oximino methyl ethyl ketone will react with nickel acetate in the presence of methylamine to form a complex very similar to that from dimethylglyoxime and derived from the imine corresponding to the ketone (XIII).

$$\text{XIII.} \quad \begin{array}{c} \text{O} \quad \text{Me} \\ \text{Me} \cdot \text{C}=\text{N} \qquad \text{N}=\text{C} \cdot \text{Me} \\ \quad \quad \text{Ni} \\ \text{Me} \cdot \text{C}=\text{N} \qquad \text{N}=\text{C} \cdot \text{Me} \\ \text{Me} \quad \text{O} \end{array}$$
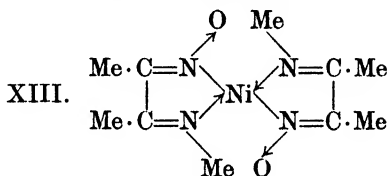
Here co-ordination with an oxygen atom is impossible because the imino group contains no oxygen, and since the complex has properties similar to those of a dioxime complex, in the latter co-ordination must be with the nitrogen atom of the oxime group.

ACYL DERIVATIVES OF HYDROXYLAMINE

The monoacyl derivatives of hydroxylamine are usually referred to as hydroxamic acids, a name which strictly refers to structure (I). They can clearly have the alternative structure (II), which should be called a hydroximic acid. In no case are the two isomers known as separate

$$\text{I.} \quad \begin{array}{c} \text{R} \cdot \text{C}=\text{O} \\ | \\ \text{NHOH} \end{array} \qquad \text{II.} \quad \begin{array}{c} \text{R} \cdot \text{COH} \\ \| \\ \text{NOH} \end{array}$$

bodies, and a compound of this class, as would be expected, can react as if it had either structure. Commonly the term hydroxamic is used to imply either of these structures, but when the hydrogen atom attached to nitrogen in (I), or the hydrogen atom of the hydroxyl group attached to carbon in (II), is replaced by an alkyl or acyl radical, the tautomerism between the two forms is no longer possible and the terms hydroxamic and

[1] *Ber.* 1929, 62, 1839.　　　　　　　　[2] Ibid. 1930, 63, 1811.

hydroximic should be used in their strict sense. The compounds are related to amides in the same way as hydroxylamine is related to ammonia.

The more important ways for obtaining both aliphatic and aromatic hydroxamic acids are:

(1) By the action of hydroxylamine on the ester of a carboxylic acid. With the simpler fatty acids this reaction takes place readily at room temperature, rather like the action of ammonia on esters; to prepare an aromatic compound such as benzhydroxamic acid, ethyl benzoate in alcoholic solution is boiled with its equivalents of hydroxylamine and of sodium ethoxide.

(2) By the action of acid anhydrides on hydroxylamine. The normal product is the O,N-diacylhydroxylamine, $R \cdot CO \cdot NH \cdot OCO \cdot R$,[1] which is easily hydrolysed by alkalis (baryta is the usual reagent) to the hydroxamic acid, $R \cdot C(OH):NOH$.

(3) By the action of hydroxylamine on an amide. For aliphatic compounds hydroxylamine hydrochloride can be used,[2] while for aromatic compounds the free base is better.

The formation of hydroxamic acids from aliphatic nitro-compounds is discussed below (see p. 235). They are also formed in the oxidation of aldoximes by Caro's acid, and also of amines of the type $R \cdot CH_2 \cdot NH_2$, since these give aldoximes as the first product of their oxidation.

The hydroxamic acids are solids, and both the aliphatic and aromatic compounds are fairly soluble in water; they are readily hydrolysed by mineral acids to hydroxylamine and a carboxylic acid. They are weak acids; acethydroxamic acid, $CH_3 \cdot C(OH):NOH$, gives a neutral solution, its dissociation constant being $2 \cdot 8 \times 10^{-8}$ at 25°, but benzhydroxamic acid is acid in reaction. Of their salts the most characteristic is the ferric salt which gives dark cherry-red solutions and is used for recognizing the presence of a compound of this type. The ferric salt of acethydroxamic acid has been studied by A. Hantzsch and C. H. Desch.[3] It is not a true salt because in solution it reacts only very slowly with ammonia to give ferric hydroxide; its formula is $Fe(C_2H_4O_2N)_3$ and it is clearly a co-ordination compound in which iron has the co-ordination number six. Its structure is most probably (III a) or (III b).

III a. Me·C—OH ... Fe b. Me·C===O ... Fe
          N—O   NH—O
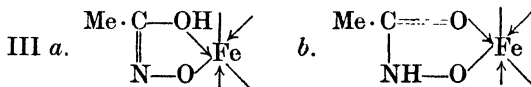
The decomposition of hydroxamic acids on heating and also of their salts and esters is accompanied by a rearrangement, usually called the Lossen rearrangement, in which the group attached to carbon migrates to the nitrogen atom. Thus benzhydroxamic acid on heating gives a mixture of carbon dioxide, aniline, and phenyl isocyanate, $\phi N:CO$; in the the latter products the phenyl group is attached to nitrogen and a re-

[1] A. Miolati, *Ber.* 1892, **25**, 699.

[2] C. Hoffmann, ibid. 1889, **22**, 2854.   [3] *Annalen*, 1902, **323**, 23.

arrangement of the Beckmann type must have taken place. A possible mechanism is:[1]

$$\phi \cdot \underset{\substack{\| \\ NOH}}{C}{-}OH \quad \longrightarrow \quad \left[\underset{\substack{\| \\ N \cdot \phi}}{HO \cdot C \cdot OH} \right] \quad \longrightarrow \quad \phi \cdot NCO + H_2O \quad \longrightarrow \quad \phi NH_2 + CO_2.$$
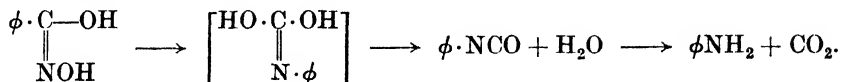
Rearrangements of this type take place quite readily when thionyl chloride is added,[2] a fact which recalls the efficiency of inorganic acid chlorides in causing the Beckmann rearrangement of oximes. The hydroxamic acids are rapidly attacked by bromine with complete decomposition to the carboxylic acid and nitrous oxide:[3]

$$2\,R \cdot CO \cdot NHOH + 2Br_2 + H_2O \;=\; N_2O + 2R \cdot CO_2H + 4HBr.$$
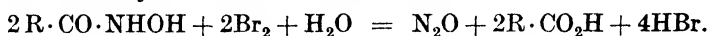
A somewhat similar decomposition takes place with bromic acid,

$$R \cdot CO \cdot NHOH + HBrO_3 \;=\; R \cdot CO_2H + HBr + HNO_3,$$
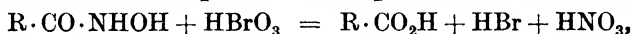
and this reaction can be used for the volumetric estimation of solutions of hydroxamic acids;[4] a known volume of a standard solution of potassium bromate is added to the hydroxamic acid solution which has been acidified with hydrochloric acid; after 30 minutes the excess of bromate is measured by adding potassium iodide and titrating with thiosulphate.

The hydroximic chlorides of structure (IV) are somewhat unstable compounds obtained by chlorination of the aldoximes:

$$R \cdot CH:NOH \;\longrightarrow\; R \cdot CCl:NOH \quad (IV).$$
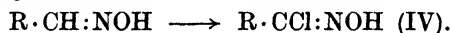
In some cases the first product of this reaction is a chloronitroso compound which rearranges to the hydroxamic chloride:[5]

$$R \cdot CHCl \cdot NO \;\longrightarrow\; R \cdot CCl:NOH.$$
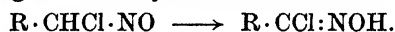
They can also be obtained from the aliphatic nitro compounds (see p. 235). They decompose readily to a variety of products, some of which are derived from the nitrile oxide formed from them by loss of hydrogen chloride (see p. 344). The simplest member of this class is formhydroximic chloride, which is the product of the addition of hydrogen chloride to fulminic acid:

$$CNOH + HCl \;\longrightarrow\; HCCl:NOH.$$
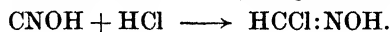
The products formed by substituting one or both hydrogen atoms of the hydroxamic acid group by hydrocarbon or acyl radicals can be divided into six types and their nomenclature is somewhat confusing. In these compounds the distinction between the terms hydroxamic and hydroximic should be strictly preserved.
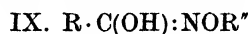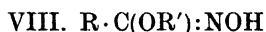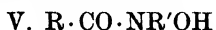
V. $R \cdot CO \cdot NR'OH$	VIII. $R \cdot C(OR'):NOH$
VI. $R \cdot CO \cdot NHOR''$	IX. $R \cdot C(OH):NOR''$
VII. $R \cdot CO \cdot NR'OR''$	X. $R \cdot C(OR'):NOR''$
Hydroxamic derivatives.	Hydroximic derivatives.

[1] E. C. Franklin, *Chem. Rev.* 1934, **14**, 244; see also E. S. Wallis and R. D. Dripps, *J. Amer. C. S.* 1933, **55**, 1701.

[2] R. Marquis, *C.r.* 1906, **143**, 464.   [3] I. de Paolini, *Gazz.* 1926, **56**, 757.

[4] R. Junell, *Arkiv f. Kemi*, 1934, **11** B, No. 30.

[5] O. Piloty and H. Steinbock, *Ber.* 1902, **35**, 3114.

The system proposed by A. Werner[1] is most commonly used; in this the name of the substituent R', as in (V) and (VIII), is placed in front of the name of the acid, while compounds such as (VI) and (IX) are described as an ether or an ester according to whether the radical R″ is alkyl or acyl. Thus the compound $\phi \cdot CO \cdot N\phi \cdot OEt$ is phenylbenzhydroxamic ethyl ether and $\phi \cdot C(OEt):N \cdot O \cdot COCH_3$ is ethylbenzhydroximic acetate. Compounds of the structures (VI) and (IX) are, of course, tautomeric; in the remaining types (V, VII, VIII, and X) the mobile hydrogen atom has been replaced and there is no tautomerism. The esters of the type (VIII) (R' = acyl) are unstable and often pass irreversibly into those of type (IX); thus benzoyl benzhydroximic acid changes into benzhydroximic benzoate. The ethers of type (VIII) (R' = alkyl) are stable.

One of the better-known compounds of this group is the so-called dibenzhydroxamic acid, more properly benzhydroximic benzoate, $\phi \cdot C(OH):N \cdot O \cdot CO\phi$, which is readily obtained by benzoylation of hydroxylamine or of benzhydroxamic acid; it is also formed in the distillation of phenylnitromethane under ordinary pressure.[2] It is a somewhat strong acid and is readily hydrolysed by alkalis to benzhydroxamic acid. Its potassium salt undergoes the Lossen rearrangement in solution[3] yielding benzoic acid and phenyl isocyanate, and in addition N,N'-diphenylurea which arises from the interaction of the isocyanate and aniline, its hydrolysis product.

One point of interest displayed by these substituted hydroxamic acids is the stereoisomerism which many of them show.[4] In compounds of types (VIII) and (X) which contain carbon doubly bound to nitrogen, the occurrence of geometrical isomerism might be expected as in the oximes. Type (IX), on the other hand, should not give rise to separable isomers because the compounds are tautomeric with type (VI) in which there is no double bond between carbon and nitrogen, and this should provide a ready method of interconversion of the stereoisomers. These conclusions are fully borne out by experiment; compounds such as ethyl-benzhydroximic acid were known to occur in two forms several years before isomeric oximes had been obtained.[5] On the other hand, in spite of exhaustive research, no compound of type (IX) is known in more than one form.[6] The behaviour of these isomeric pairs has not been studied in great detail. The action of hydroxylamine on benzimino-ethyl ether gives two isomeric benzhydroximic acids which can be separated by fractional crystallization (m.ps. 54° and 68°). Of these the lower-melting undergoes a typical Beckmann rearrangement with phosphorous penta-chloride to give a urethane, while the isomeric β-acid suffers no rearrange-

[1] *Ber.* 1892, **25**, 28.

[2] F. Heim, ibid. 1910, **43**, 3417.

[3] See E. Mohr, *J. pr. Chem.* 1905, **71**, 133.

[4] A detailed account will be found in J. Meisenheimer, *Stereochemie*, ed. Freudenberg, Leipzig 1933, p. 1090 et seq.

[5] W. Lossen, *Annalen*, 1875, **175**, 282, 326.   [6] A. Werner, *Ber.* 1892, **25**, 35.

ment but forms a phosphoric ester. On the assumption of a *trans*-migration, the reaction of the α-form will be:

$$\phi-\underset{\underset{NOH}{\parallel}}{C}-OEt \longrightarrow HO-\underset{\underset{N\phi}{\parallel}}{C}-OEt \longrightarrow \underset{\diagdown NH\phi}{\overset{\diagup OEt}{CO}} \qquad XI. \qquad EtO\cdot\underset{\underset{NOH}{\parallel}}{C}\cdot\phi$$
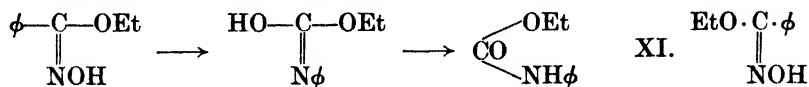
while the configuration of the β-form will be that shown in (XI). If the β-form were to undergo rearrangement, it would mean the exchange of hydroxyl and ethoxyl groups, and it may well be that the great similarity between these groups is the reason why no rearrangement takes place; if they did exchange, the compound would be of much the same energy content as before.[1]

The amides of hydroxamic acids are usually referred to as amidoximes, or sometimes as hydroxyamidines. They are of the structure $R\cdot C\overset{\diagup NH_2}{\diagdown NOH}$ which is tautomeric with $R\cdot C\overset{\diagup NH}{\diagdown NHOH}$. In the aliphatic series they are best obtained by the action of hydroxylamine on a nitrile.

$$R\cdot CN + H_2NOH \longrightarrow R\cdot C\overset{\diagup NH}{\diagdown NHOH}$$
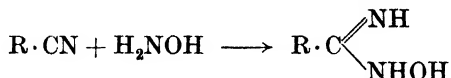
The aromatic members are prepared by the action of hydroxylamine on the thioamides or amidines. They are both basic and acidic, giving stable salts with acids and less stable salts with bases. They are easily hydrolysed, sometimes by water alone, to the amide and hydroxylamine. With phosphorus pentachloride they undergo the Beckmann rearrangement to give substituted ureas.

$$R\cdot\underset{\underset{NOH}{\parallel}}{C}\cdot NH_2 \longrightarrow HO\cdot\underset{\underset{NR}{\parallel}}{C}\cdot NH_2 \longrightarrow \underset{\diagdown NHR}{\overset{\diagup NH_2}{CO}}$$
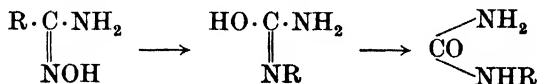
The simplest amidoxime, formamidoxime, $HC(NH_2){:}NOH$, can be obtained from prussic acid. It is isomeric with urea and is called isouretin. Geometrical isomerism would not be expected to show itself in the amidoximes themselves or in their substitution products of the type $R\cdot C(NHR){:}NOH$ because, as above, tautomerism with the form

$$R\cdot C({:}NH)\cdot NHOH$$
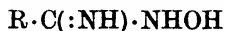
will allow ready interconversion of the two stereoisomers. In the N,N-di-substituted amidoximes, $R\cdot C(NR_2){:}NOH$, tautomerism is impossible and geometrical isomers might occur. A search for them has, however, proved unsuccessful.[2]

Note on Free Rotation

The phrase free rotation is unfortunate in some ways, because it is apt to convey a false impression. What is really implied by the terms free rota-

[1] A. Werner, *Ber.* 1892, **25**, 33; 1893, **26**, 1565.
[2] O. L. Brady and F. H. Peakin, *J.C.S.* 1929, 2267.

tion and the inhibition of free rotation can be best understood by thinking of a molecule of the type abdC—Cabd and considering the energy content which corresponds to a series of positions obtained by keeping one half of the molecule stationary and allowing the other half to rotate about the bond between the carbon atoms.[1] The shape of the curves obtained by plotting the energy against the angle through which rotation has taken place, measured from some arbitrary zero, will be of different types according to the nature of the groups a, b, and d. If these are such that they have no mutual effects upon one another, the curve will be of the type (I), in which all positions have the same energy and are thus equally probable. If, on the other hand, the molecule is of the type of dibenzyl, ϕCH_2—$CH_2\phi$, the curve will be of the type (II), in which one position has a smaller energy than all others, and is thus more probable, and the majority of the molecules will be in that configuration or will be oscillating about it.
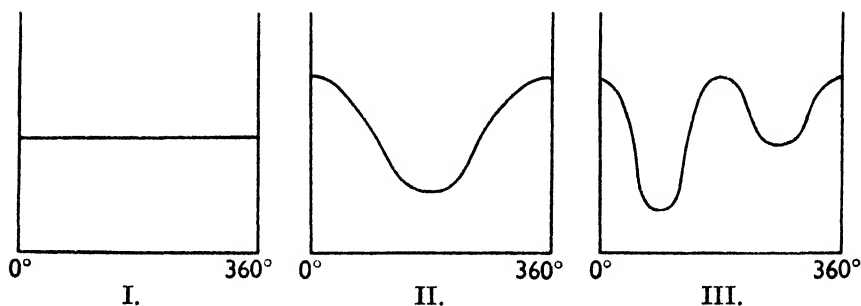
The reason for the existence of such a minimum is the forces between the groups attached to the carbon atoms. These forces are in part the interactions between the electrical moments associated with the linkages and in part purely steric forces, and their magnitude clearly depends on the distances between the groups, that is, on the angle used as abscissa in the figures. The actual shape and position of the curve depends, of course, on the particular compound, and temperature has a great effect on the actual configuration of the molecule. At high temperatures the molecule will possess high rotational energy, the interactions between groups will be of little consequence, and all configurations will tend to an equal probability. Free rotation does not necessarily mean that there is a perpetual state of rotation of one half of the molecule with respect to the other; this may be true at high temperatures, but at the lower temperatures it may mean that there is one and only one preferred configuration, i.e. one minimum on the potential-energy curve.

In the case of a molecule of the type $\overset{a}{\underset{b}{>}}C{=}C\overset{a}{\underset{b}{<}}$, the potential energy curve is of type (III). Of the possible configurations obtained by rotating one half of the molecule with respect to the other about the double bond,

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[1] Cf., *inter alia*, A. R. Olson, *Trans. Faraday Soc.* 1931, **27**, 69.

there are two which correspond to minima of potential energy. Each of these is within limits a stable state in that if a small distortion from either state is set up, there will be a tendency to revert to the state, since such reversion is accompanied by decrease in potential energy; one state, however, is more stable than the other, because it corresponds to a lower energy content. The change from the less stable of the two states to the more stable will not be spontaneous at low temperatures; a molecule must first be activated so that it may pass through the position corresponding to a maximum on the energy curve. The difference in the two minima corresponds to the heat of transformation of one form into the other. Such a picture is an elegant summary of what we know about such molecules. 'Inhibition of free rotation' does not mean that rotation never takes place: it means rather that there are two configurations of minimum potential energy.

NITROSO COMPOUNDS

THE nitroso compounds proper contain the nitroso group —N=O attached to a carbon atom. They are not a large class but present several interesting peculiarities. Two of these serve to distinguish them sharply from the nitrosamines, the compounds in which the group —N=O is attached to a nitrogen atom, and which are discussed later. These are, first, the blue or green colour of the true monomolecular nitroso compounds in all states of aggregation, which arises from the characteristic absorption of the $\geq$C—N=O group in the yellow and red region of the spectrum, and, second, the tendency of the compounds to associate, to a greater or less extent according to the nature of the other groups in the molecule, to colourless bimolecular complexes. The structure of these complexes is discussed below: they are formed by the chemical interaction of the nitroso groups of the two molecules with each other.

Very few true nitroso compounds are known which contain the nitroso-group attached to a primary or secondary carbon atom. In the large majority of cases attempts to prepare such compounds result in the formation of an oxime; the group —CH$_2$·NO or $\geq$CH·NO nearly always changes irreversibly into the group —CH:NOH or $\geq$C:NOH. Thus the majority of nitroso compounds are tertiary. The exceptional secondary compounds will be discussed separately.

The principal methods for preparing both aliphatic and aromatic nitroso compounds are the oxidation of amines and of N-substituted hydroxylamines. The two oxidations differ from one another in several respects.

(1) *Oxidation of Amines*

As has been mentioned earlier (p. 53), oxidizing agents fall into two sharply distinguished classes in their effect on amines. With the one class the first action is the removal of hydrogen to give a free radical which then undergoes various changes, and with the other it is the addition of oxygen to give a substituted hydroxylamine, very probably via an unstable primary amine oxide: ϕNH$_2$ $\longrightarrow$ ϕNH$_2$O $\longrightarrow$ ϕNHOH. The nitroso compound is formed by the further oxidation of the hydroxylamine, and thus the majority of oxidizing agents, which belong to the first class and give no hydroxylamine, are useless for the preparation of nitroso compounds. Even with the right choice of agent the conditions of the reactions must be chosen with care, because the nitroso compounds are not very stable. Thus oxidation in markedly alkaline solution is impossible since under those conditions nitroso compounds condense with hydroxylamines (especially in the aromatic series) to form azoxy compounds (see pp. 253

and 427). The best oxidizing agent for the purpose is permonosulphuric acid (Caro's acid, H_2SO_5), which, as E. Bamberger showed,[1] is a general reagent for oxidizing aliphatic primary amines in which the amino group is attached to a tertiary carbon atom, and also primary aromatic amines, to nitroso compounds. Perdisulphuric acid, $H_2S_2O_8$, belongs to the other class of oxidizing agents[2] and gives no nitroso compounds, and it was through this difference that Caro first discovered the change of ordinary persulphuric acid into Caro's acid. The oxidation proceeds at room temperature, but because of the sensitive character of nitroso compounds the yields are seldom good. Perbenzoic acid, $\phi \cdot CO \cdot O_2H$, can also be used as oxidizing agent.

(2) *Oxidation of Mono-N-substituted Hydroxylamines.*

This general method of preparation involving the change of

$$R \cdot NHOH \longrightarrow R \cdot NO$$
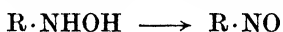
has been used in both the aliphatic and aromatic series. The starting-point is usually the nitro compound which can be obtained even in the aliphatic series by direct nitration, since an aliphatic hydrocarbon containing a tertiary hydrogen atom ($\geqslant CH$) is fairly readily nitrated. In the reduction of a nitro compound the nitroso compound is an intermediate stage (see p. 253), but, because of the ease with which it is reduced further, it is almost impossible to isolate it in quantity. Hence the reduction is taken to the stage of the hydroxylamine which can be isolated, and this is oxidized to the nitroso compound:

$$\phi NO_2 \longrightarrow \phi NHOH \longrightarrow \phi NO.$$

The choice of oxidizing agent is not of such vital importance here, although for the reasons given above alkaline reagents are useless and excess of a vigorous oxidizing agent would carry the oxidation to the nitro stage; aqueous chromic acid (dilute sulphuric acid and potassium bichromate) is usually employed, and sometimes ferric chloride. Nitrobenzene can be converted into nitrosobenzene by electrolytic reduction in a cell without any diaphragm separating kathode and anode and with a neutral electrolyte such as sodium sulphate.[3] The process is not direct reduction to the nitroso compound: the nitrobenzene is reduced at the kathode to the hydroxylamine which is oxidized to the nitroso compound at the anode.

By the first of these methods nitroso-tertiary-butane, $(CH_3)_3C \cdot NO$, the simplest nitroso compound known, can be prepared in very small yield from tertiary-butylamine.[1] Its behaviour is typical of the aliphatic nitroso-hydrocarbons. It forms colourless prisms which are surprisingly volatile: if left standing in the air for a short time it disappears, and if

[1] E. Bamberger and R. Seligman, *Ber.* 1903, **36**, 685.

[2] S. Goldschmidt, ibid. 1920, **53**, 35.

[3] O. Dieffenbach, *Zent.* 1908, i, 911.

heated in an open tube it vanishes at about 76° without melting or boiling. Its vapour pressure clearly becomes greater than the atmospheric pressure below the melting-point. If heated in a sealed tube, it melts to a deep blue liquid, which at 80–82° volatilizes to the cooler parts of the tube and condenses to deep blue drops which solidify to colourless crystals. If an ethereal solution of the compound is distilled, the whole of it goes over with the ether vapour. It is readily soluble in most organic solvents. The solutions are colourless at first, but change to a deep blue, gradually on standing and more rapidly on warming. This change in colour is accompanied by a change in molecular weight which can be observed with benzene as solvent by the freezing-point of the solution. In the colourless solution the molecular weight of the solute is twice that required by the simple formula $(CH_3)_3C \cdot NO$, but, as the colour deepens, it gets smaller and ultimately reaches the value which corresponds to the simple formula. The same difference in molecular complexity between the colourless and coloured forms has been observed for several other aliphatic nitroso compounds where the change of the first into the second is slow. In most cases the colourless solutions are odourless, but the blue solutions have a characteristic biting smell.

Nitrosobenzene, a typical aromatic nitroso compound, is usually prepared by the second of the above methods and separated from the other products by distillation with steam, in which it is very volatile. It can be crystallized from alcohol, and melts to an emerald-green liquid at about 68°; the melting-point of no aromatic nitroso compound is sharp when observed by the ordinary method, because it dissociates to some extent to single molecules as it melts, so that its latent heat of fusion includes the quite considerable heat of dissociation, and is much larger than for a normal substance. It is readily soluble in nearly all solvents and the solutions are immediately emerald-green in colour. They contain the substance almost entirely as simple molecules, as has been shown by freezing-point measurement of solutions in benzene, acetic acid, acetone, and naphthalene. The rate of depolymerization is much greater than with the aliphatic compounds, and it is not possible to find the molecular weight of the colourless molecules in solution as with some of the aliphatic compounds. There is, however, good reason for believing that the colourless form is a bipolymer, as in the aliphatic series. Nitrosobenzene forms colourless solid solutions in nitrobenzene, and from the melting-points of mixtures of the two the molecular weight in the solid solution can be calculated and is twice that of the simple molecule.[1] Further, although nitrosobenzene seems to be practically entirely in the monomolecular form in benzene,[2] introduction of substituents, particularly if they are in the ortho positions, changes the behaviour and quite a high percentage of the compound exists in a colourless form in solution. This effect is shown in the following table, which gives the percentage association, bimolecular

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[1] C. Drucker and T. Flade, *Z. wiss. Photograph.* 1930, **29**, 29.

[2] D. Ll. Hammick, *J.C.S.* 1931, 3105.

association being assumed, in 1 mol. per cent. solution in benzene at the freezing-point.

$$\underset{18\%}{\text{Br}\!-\!\!\!\bigcirc\!\!\!-\!\text{Br, Br, NO}} \qquad \underset{61\%}{\text{NO}_2,\ \text{NO}} \qquad \underset{88\%}{\text{CH}_3,\ \text{CH}_3,\ \text{NO}} \qquad \underset{80\%}{\text{CH}_3,\ \text{CH}_3,\ \text{CH}_3,\ \text{NO}}$$
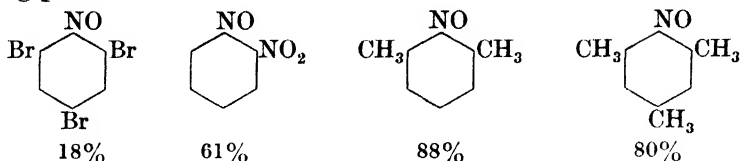
The equilibrium between the two forms alters with temperature and it is possible to determine how many molecules are involved in the association by measuring the amount of the coloured form at not less than three different temperatures. The measurements have been carried out in the case of nitroso-mesitylene, the last of the four compounds above, and show that the complex contains two of the simple molecules.[1]

Of the other known methods of obtaining nitroso compounds two are particularly interesting because they give rise to products which present the extremes in the stability of the bimolecular form. The first of these is the action of an alkyl nitrite on certain ketones in the presence of hydrogen chloride. As has been discussed earlier (p. 171), from a ketone such as acetone, the oximino-ketone, $CH_3 \cdot CO \cdot CH{:}NOH$, can be obtained in this way. If the ketone contains a tertiary carbon atom next to the carbonyl group, as in methyl isopropyl ketone, $(CH_3)_2CH \cdot CO \cdot CH_3$, the product of the reaction is a mixture consisting mainly of the oximino compound formed by attack on the methyl group, and partly of methyl-nitroso-isopropyl ketone, $Me_2C(NO) \cdot CO \cdot Me$, formed by attack on the isopropyl group.[2] The nitrosoketones obtained in this way are colourless solids which give colourless solutions, and the freezing-points of the benzene solutions show that they exist in the bimolecular form, as the absence of colour would indicate. At room temperature there is no tendency for this form to dissociate, but if the solutions are heated, they slowly become bluish green, and on cooling the colour slowly disappears again. The great stability of the bimolecular form in these compounds makes them of importance in the discussion of the structure of that form (see below). The stability is connected in some unknown way with the presence of the carbonyl group in the α-position to the nitroso group; the β-carbonyl compound nitroso-isopropylacetone, $Me_2C(NO) \cdot CH_2 \cdot COMe$, behaves like the majority of aliphatic nitroso compounds and depolymerizes in solution.

At the other extreme there are nitroso compounds in which the bimolecular form is unknown. The most striking of these are the chloro- (or bromo-) nitrosoparaffins which O. Piloty prepared by the action of the halogen on aliphatic ketoximes in the presence of pyridine.[3] From acetoxime and bromine, for example, 2-bromo-2-nitrosopropane can be obtained:

$$(CH_3)_2C{:}NOH + Br_2 \longrightarrow (CH_3)_2CBr \cdot NO + HBr.$$
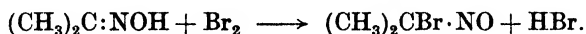
[1] C. K. Ingold and H. A. Piggott, J.C.S. 1924, 125, 168.

[2] J. G. Aston, D. F. Menard, and M. G. Mayberry, J. Amer. C. S. 1932, 54, 1530; 1935, 57, 1888.   [3] Ber. 1898, 31, 452.

This is a mobile liquid of an ultramarine blue colour which freezes at a low temperature to blue crystals and boils at about 83° to give a blue vapour, which has a powerfully unpleasant smell resembling at the same time bromine and acrolein. There is no indication of the existence of a colourless polymer under any conditions. The compound is somewhat unstable and decomposes on standing into a variety of products. A very interesting extension of this reaction is to the dioxime of cyclohexa-1,4-dione (I).[1] Chlorine in the presence of hydrochloric acid converts this
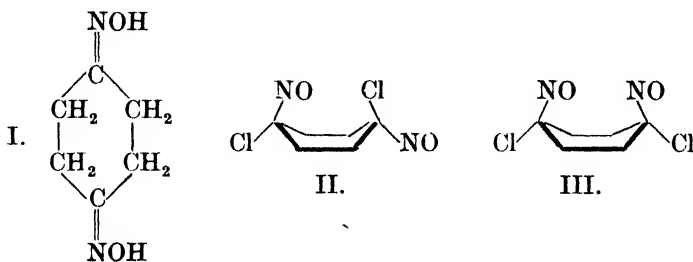
compound into a dichloro-dinitroso compound, but two isomeric products are obtained which can be separated by taking advantage of their great difference in solubility in ether. The more soluble compound forms blue crystals which melt at 108°, and show a normal molecular weight in solution. If left to stand in alcoholic solution, this substance is transformed into the less soluble product formed in the preparation: the change is faster in acetic acid which contains some hydrogen chloride. This second product is colourless, decomposes indistinctly at 160–165°, and in solution in phenol has the same simple molecular weight as the first compound. If its solution in methyl alcohol is warmed, a blue colour appears which vanishes on cooling. This is not due to the regeneration of the blue isomer, because the colour disappears at once on cooling, and because the change from the blue to the colourless isomer is slow. It is clear that a compound of the structure of a 1,4-dichloro-1,4-dinitrosocyclohexane can exist in two stereoisomeric forms, and that in the *trans* form (II) the nitroso groups will lie on opposite sides of the ring, while in the *cis* form (III) they are on the same side and, as the space-arrangement of the carbon atoms of the cyclohexane ring is changed by thermal impacts, close approach of the nitroso groups is very probable. Thus it seems that the blue isomer is the *trans* compound (II: which is an attempt to represent one out of the many possible configurations of the cyclohexane ring), in which the two nitroso groups are so arranged in space that they cannot interact, while the colourless isomer is the *cis* compound (III). The case is somewhat similar to the two cyclohexane-1,4-dicarboxylic acids, of which only the *cis* compound can form a monomolecular anhydride.[2]

Piloty's reaction for the preparation of halogen substituted nitroso

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[1] O. Piloty and H. Steinbock, *Ber.* 1902, **35**, 3101.
[2] R. Malachowski and J. Jankiewiczówna, ibid. 1934, **67**, 1783.

compounds does not take place with all ketoximes.[1] If in a ketoxime, $R \cdot C:NOH \cdot R'$, the group R is a phenyl or substituted phenyl, a cyano group or a carboxyl group, no nitroso compound is formed: for this to take place, at least one of the groups R and R' must be an alkyl group or carbethoxy group. No satisfactory explanation of these facts is known. Aromatic nitroso compounds have been obtained in good yield by the action of nitrosyl chloride on aryl magnesium halides:

$$\phi MgBr + NOCl \longrightarrow \phi NO + MgBrCl.$$
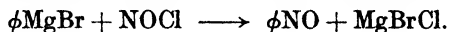
The nitrosophenols and nitrosoanilines are discussed separately below.

The chemical reactions of the nitroso group have been mainly investigated in the case of nitrosobenzene, which is the most accessible member of the class. They are not very stable compounds and undergo decomposition to give a large variety of products under the action of light, of alkalis, and of acids. Bamberger has investigated the products obtained from nitrosobenzene in great detail; as an example of the scale on which he worked it may be mentioned that in a single set of experiments[2] on the action of alkali at 100°, 1,330 gm. of nitrosobenzene were heated with alkali under pressure in 19 champagne bottles and 12 different decomposition products were isolated and identified. The principal product was azoxybenzene; the remainder included nitrobenzene, aniline, o- and p-aminophenol, prussic acid, and ammonia. The nitroso group can be oxidized to the nitro group, best with hydrogen peroxide, and can be reduced to the amino group by stannous chloride or zinc and acetic acid, although the yields of amine are small. Catalytic reduction of nitrosobenzene by hydrogen in the presence of palladium (on calcium carbonate) gives a quantitative yield of azobenzene, $\phi N:N\phi$, probably by condensation of aniline with unchanged nitrosobenzene.[3] The group behaves in some ways very like the carbonyl group in the condensation reactions which it shows. Nitrosobenzene reacts with hydroxylamine to give benzenediazo-hydroxide,[4] with aromatic primary amines to give azo compounds,[5] with phenylhydroxylamine to give azoxybenzene, and with certain compounds containing a reactive methylene group to give anils.[6]
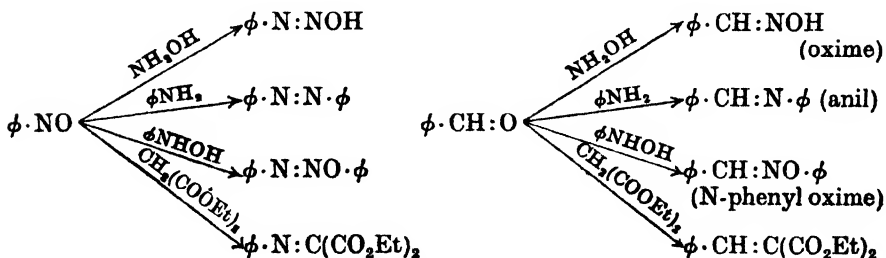
[1] I. de Paolini, *Gazz.* 1931, 61, 551.   [2] *Ber.* 1900, 33, 1939.
[3] M. Busch and K. Schulz, ibid. 1929, 62, 1466.
[4] A. Hantzsch, ibid. 1905, 38, 2056.
[5] H. Wieland, ibid. 1915, 48, 1107.   [6] T. K. Walker, *J.C.S.* 1924, 125, 1623.

With substituted hydrazines, however, the product is not a diazoamino compound, as would be expected on this analogy. Condensation of the aldol type seems first to take place, and the product then reduces more nitrosobenzene to phenylhydroxylamine, being itself oxidized:[1]

$$\phi \cdot NO + H_2N \cdot NHR \longrightarrow \phi \cdot N(OH) \cdot NH \cdot NH \cdot R \longrightarrow \phi \cdot N(OH) \cdot N:N \cdot R.$$
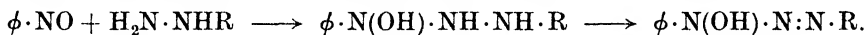
The latter compound is tautomeric with $\phi \cdot NO:N \cdot NHR$.

The last stage of this reaction is similar to the action of hydrazobenzene on nitrosobenzene, when azobenzene and phenylhydroxylamine are produced quantitatively:

$$\phi \cdot NH \cdot NH \cdot \phi + \phi \cdot NO \longrightarrow \phi \cdot N:N \cdot \phi + \phi \cdot NHOH.$$
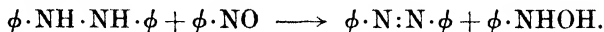
Other reactions of nitrosobenzene that may be mentioned are:

(a) With aliphatic diazo compounds N-phenyl-oximes are formed:[2]

$$R_2CN_2 + \phi \cdot NO \longrightarrow R_2C:N\phi \rightarrow O + N_2.$$
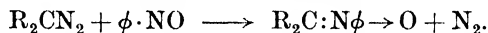
(b) With ketenes an addition product is formed which seems to have a four-membered ring structure (I) and which on heating decomposes into a ketone and phenyl isocyanate.[3] In the same reaction a second complex is also formed, and to this the alternative four-membered-ring structure (II) has been allotted. It decomposes in the cold into carbon dioxide and an anil, just as a β-lactone breaks up readily into carbon dioxide and an olefine.

$$
\text{I.} \quad
\begin{array}{c}
\phi_2C\text{—}CO \\
| \qquad | \\
O\text{—}N\cdot\phi
\end{array}
\longrightarrow
\begin{array}{c}
\phi_2C \quad CO \\
\| \qquad \| \\
O \qquad N\cdot\phi
\end{array}
\qquad
\text{II.} \quad
\begin{array}{c}
\phi_2C\text{—}CO \\
| \qquad | \\
\phi N\text{—}O
\end{array}
\longrightarrow
\begin{array}{c}
\phi_2C \\
\| \\
\phi N
\end{array} + CO_2
$$

$$
\begin{array}{c}
R_2C\text{—}CO \\
| \qquad | \\
R_2C\text{—}O
\end{array}
\longrightarrow
\begin{array}{c}
R_2C \\
\| \\
R_2C
\end{array} + CO_2
$$
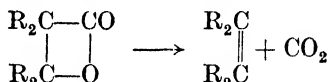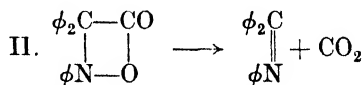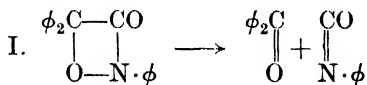
Some of the aliphatic nitroso compounds are decomposed by light, the nitroso group splitting off together with a hydrogen atom from the neighbouring carbon atom to give hyponitrous acid or its decomposition products, while an unsaturated compound remains. Thus nitroso-isopropylacetone gives mesityl oxide:[4]

$$Me_2C(NO) \cdot CH_2 \cdot COMe \longrightarrow Me_2C:CH \cdot COMe + \tfrac{1}{2}H_2N_2O_2.$$
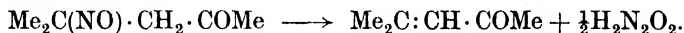
The reaction is not general to all nitroso compounds, but only seems to take place when the quantum of energy absorbed in the red, the typical position for the absorption band of these compounds, is large enough to provide the necessary heats of rupture of the links involved.

As has been mentioned, the majority of nitroso compounds contain the nitroso group attached to a tertiary carbon atom, because the primary and secondary compounds usually rearrange very rapidly to oximino

[1] E. Bamberger, *Helv. Chim. Acta*, 1931, 14, 242.
[2] H. Staudinger and K. Miescher, ibid. 1919, 2, 554.
[3] H. Staudinger and S. Ielagin, *Ber.* 1911, 44, 365.
[4] K. D. Anderson and D. Ll. Hammick, *J.C.S.* 1935, 30, 1369.

compounds. This tendency is so strong that cases are known where part of the molecule is eliminated in order that the oximino structure may be formed. An example is one of the stages in the classical synthesis of glycerol by O. Piloty and O. Ruff.[1] In this formaldehyde and nitromethane were condensed together and the product reduced to a hydroxylamine. When this was oxidized with mercuric oxide, instead of the nitroso compound which might be expected, formaldehyde was eliminated and the oxime of dihydroxyacetone formed. This was converted into glycerol by hydrolysis and reduction:

$$3CH_2O + H_3C \cdot NO_2 \longrightarrow (HOCH_2)_3C \cdot NO_2 \longrightarrow (HOCH_2)_3C \cdot NHOH$$
$$\longrightarrow CH_2O + (HOCH_2)_2C:NOH$$
$$\longrightarrow (HOCH_2)_2CHOH.$$
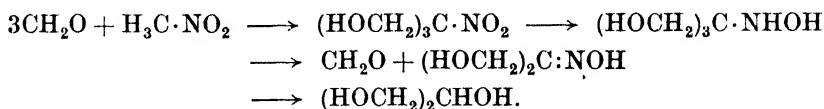
A few cases are known, however, in which the rate of change,

$$>CH \cdot NO \longrightarrow >C:NOH,$$
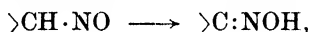
is slow so that true secondary nitroso compounds can be isolated. There are two classes of such compounds known. The first consists of chloronitroso-paraffins of the general formula $R \cdot CHCl \cdot NO$; these can be obtained by Piloty's reaction, the action of chlorine on an aliphatic aldoxime in the presence of hydrogen chloride,[2] and also in small yield by the action of nitrosyl chloride on an aliphatic aldoxime:[3]

$$CH_3 \cdot CH:NOH + 2NOCl \longrightarrow CH_3 \cdot CHCl \cdot NO + HCl + 2NO.$$

1,1-Chloronitrosoethane forms colourless crystals which dissolve in liquid hydrogen cyanide at —10° to a colourless solution in which it is bimolecular. It melts at 65° to a deep blue liquid and its solutions in organic solvents at room temperature are blue. It is clearly a true nitroso compound, but if its solutions are warmed, or if the substance is kept at its melting-point, it is converted into the isomeric hydroxamic chloride, $CH_3 \cdot CHCl \cdot NO \longrightarrow CH_3 \cdot CCl:NOH$. The aromatic aldoximes, with one exception, do not give such nitroso compounds, but are converted either by chlorine or nitrosyl chloride directly into the hydroxamic chloride. Sometimes there is a transient green or blue colour during the reaction, which may show that the nitroso compound is formed. The one exception is the oxime of piperonal.[4]

The second class of secondary nitroso compounds are the nitrosocarboxylic esters of J. Schmidt.[5] α-Acyl esters of the general formula $R \cdot CHR' \cdot CO_2Et$, where R' is an acyl group such as acetyl and R is an alkyl group, are attacked by nitrous fumes generated from arsenious oxide and nitric acid, and converted into α-nitroso esters, $R \cdot CHNO \cdot CO_2Et$, the acyl group being eliminated. The compounds are deep blue oils which give blue solutions in organic solvents. On standing their colour disappears

[1] *Ber.* 1897, **30**, 1656, 3161.   [2] Ibid. 1902, **35**, 3101.

[3] H. Rheinboldt and M. Dewald, *Annalen*, 1927, **451**, 273.

[4] H. Rheinboldt, M. Dewald, F. Jansen, and O. Schmidt-Dumont, ibid. 1927, **451**, 161.   [5] Summarizing paper, ibid. 1910, **377**, 30.

and they are converted into yellow oils which are soluble in aqueous alkali and are the isomeric oximino esters:

$$\text{R} \cdot \text{CHNO} \cdot \text{CO}_2\text{Et} \longrightarrow \text{R} \cdot \text{C}(:\text{NOH}) \cdot \text{CO}_2\text{Et}.$$
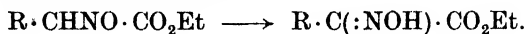
In benzene solution the molecular weight of the initially blue solution is normal, and as the colour fades it first rises to twice that value and then falls again to the normal value. This shows that the first process is slow polymerization to the bimolecular form, followed by isomeric change. In the case of nitrososuccinic ester, $\text{EtO}_2\text{C} \cdot \text{CH}_2 \cdot \text{CHNO} \cdot \text{CO}_2\text{Et}$, about three weeks is needed for completion of the change at room temperature. As would be expected for an isomeric change which involves the shift of a hydrogen atom, the rate of change is enormously accelerated by traces of alkali, as in the case of the rates of tautomeric change in keto-enol tautomers. These nitroso compounds are not tautomeric, because the change into the oximino ester is irreversible.

Secondary nitroso compounds are also formed by the action of the oxides of nitrogen on certain ethylenic hydrocarbons, a complicated subject which is discussed briefly below. One example, and that a rather strange one, of a primary nitroso compound seems to be known. If N-benzyl-hydroxylamine is oxidized with bichromate,[1] it might be expected that the product would be phenyl-nitrosomethane,

$$\phi \cdot \text{CH}_2 \cdot \text{NHOH} \longrightarrow \phi \cdot \text{CH}_2 \cdot \text{NO},$$
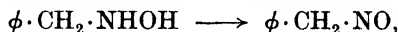
which would undergo immediate isomeric change into benzaldoxime, $\phi \cdot \text{CH}:\text{NOH}$. This is in fact formed, but in addition there are several other products and among them a colourless crystalline compound of twice the expected molecular weight. It melts to a green liquid and gives faintly green solutions, and thus appears to be the bimolecular nitroso compound, $\phi \cdot \text{CH}_2 \cdot \text{N}_2\text{O}_2 \cdot \text{CH}_2 \cdot \phi$, bisphenylnitrosomethane. This view of its structure is confirmed by the fact that it is converted into the sodium salt of benzaldoxime by long digestion with warm aqueous caustic soda. In this case the stability of the bimolecular form is so great that the isomeric change into an oxime is extremely slow. Other reactions of this curious compound are discussed below.

The polynitroso compounds have been little investigated. A compound $\text{C}_6\text{H}_4\text{N}_2\text{O}_2$ which is formed by the oxidation of o-nitraniline with hypochlorite[2] was at one time thought to be o-dinitrosobenzene; it has been shown, however, to be a benzfurazane oxide (I). The carbon ring is no longer benzenoid, but shows typical quinone properties and adds on four atoms of bromine.[3]

I.   II.
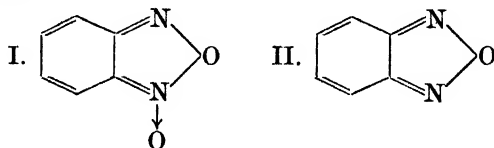
[1] R. Behrend and E. König, *Annalen*, 1891, **263**, 212.
[2] A. G. Green and F. M. Rowe, *J.C.S.* 1912, **101**, 2452.
[3] D. Ll. Hammick, W. A. M. Edwardes, and E. R. Steiner, *J.C.S.* 1931, 3308.

It is readily reduced to benzfurazane (II). m-Dinitrosobenzene has been prepared from the dinitro compound by reduction followed by oxidation[1] and behaves like a true nitroso compound, but the compound described as p-dinitrosobenzene,[2] although it has the right composition, is almost certainly no nitroso compound.

The Structure of the Nitroso Group and of the Bisnitroso Compounds

From the description of the simple nitroso compounds which has been given, it will be realized that the nitroso group when attached to a carbon atom is in some ways abnormal in its properties. There seems to be no obvious reason why the group should be so markedly different from the carbonyl group in a ketone and from the nitroso group in a nitrosamine $R_2N \cdot NO$ and in an alkyl nitrite $RO \cdot NO$. In none of these compounds is there any tendency to form a bimolecular polymer, nor is there the absorption of light in the visible region which gives the monomolecular nitroso compounds their characteristic blue or green colour. In some respects there is an analogy between a monomolecular nitroso compound and a free radical containing trivalent carbon such as triphenylmethyl, or divalent nitrogen such as the dissociation product of tetraphenyl-hydrazine (see p. 388).[3] Both classes of compounds are coloured and associate to colourless dimeric forms, the position of equilibrium between molecular and bimolecular compounds depending on temperature, solvent, and the nature of the other groups in the molecule. There are also chemical analogies. Nitric oxide, NO, which in spite of its odd-electron structure behaves in most respects in a singularly saturated fashion, combines very readily with free radicals, but not with a normal double bond as in an ethylene $>C=C<$ or a ketone $>C=O$. Nitrosobenzene in chloroform solution rapidly absorbs nitric oxide to give benzene diazonium nitrate:

$$\phi \cdot NO + 2NO \longrightarrow [\phi \cdot N_2]NO_3.$$
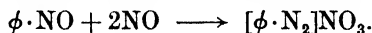
Again radicals containing divalent nitrogen and monovalent oxygen are rapidly reduced by hydrazobenzene, $\phi \cdot NH \cdot NH \cdot \phi$, which is oxidized to azobenzene. A similar reaction takes place with nitrosobenzene which is reduced to phenylhydroxylamine:

$$\phi \cdot NO + \phi \cdot NH \cdot NH \cdot \phi \longrightarrow \phi NHOH + \phi \cdot N:N \cdot \phi.$$
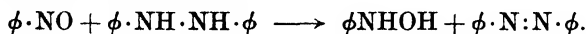
Finally the free radical triphenylmethyl is capable of uniting with other free radicals and is often used to detect their presence. Goldschmidt and Christmann found that triphenylmethyl combined readily with nitroso-benzene.

In consequence of facts such as these, it has been suggested that the nitroso group is itself a free radical and the suggestion has taken two forms: (a) that the oxygen and nitrogen atoms are linked by a single bond and the

[1] F. J. Alway and R. A. Gortner, *Ber.* 1905, **38**, 1899.

[2] R. Nietzki and F. Kehrmann, ibid. 1887, **20**, 613.

[3] S. Goldschmidt and F. Christmann, *Annalen*, 1925, **442**, 246.

formula should be written R—N̶—O̶, with divalent nitrogen and mono-valent oxygen;[1] (b) that the mode of linkage is identical with that between the two atoms of an oxygen molecule, which is known not to be an ordinary double bond composed of two two-electron links, but involves a triplet state.[2] Such suggestions are attractive at first sight, but neither of them can be accepted. Both of the suggested types of linkage involve two electrons which are not paired, and whose spin must thus give rise to paramagnetism. This is a matter of experimental fact, since the free radicals are known to differ from the vast majority of organic compounds in being paramagnetic and not diamagnetic and the oxygen molecule similarly differs from all other diatomic molecules (except nitric oxide which necessarily contains one odd electron). The nitroso compounds, however, are diamagnetic and not paramagnetic,[3] and this simple fact makes the suggested structures impossible. It may be pointed out that in the nitrites, RONO, and the nitrosamines, $R_2N \cdot NO$, the nitroso group is united to an atom which has at least one lone pair of electrons, while those of the carbon atom in a C-nitroso compound are all involved in valency formation. This fact may be connected with the distinction between the C-nitroso compounds and the other two classes.

The structure of the bisnitroso group which is present in the bimolecular form of the nitroso compounds has been the subject of much discussion and still awaits a satisfactory solution. There is no doubt that in the bimolecular compound the two nitroso groups are held together by ordinary chemical valencies. Probably the best evidence for this is the fact that in homogeneous solution depolymerization of the aliphatic bisnitroso compounds is a slow process which shows that a heat of activation is involved in the change. The case is clearly parallel to the reversible polymerizations such as those of many derivatives of cyanogen and of many unsaturated hydrocarbons (e.g. cyclopentadiene) in which the polymer is a compound of definite chemical structure which is different from that of the monomolecular parent.

In the majority of cases a direct inquiry by chemical means into the structure of the bisnitroso group is impossible because of the ease with which it dissociates into two simple nitroso groups. It is for this reason that the compounds described above in which the bimolecular forms are exceptionally stable and do not dissociate in solution at room temperature, are of exceptional interest; in these cases ordinary means can be used to discover the structure. Methyl α-nitroso-isopropyl ketone (see p. 207) is a case in point: this compound gives colourless solutions which only become faintly blue at high temperatures. If it is reduced at room temperature with stannous chloride and hydrochloric acid, the products are hydrazine and methyl isopropyl ketone.[4]

$$CH_3 \cdot CO \cdot CMe_2 \cdot N_2O_2 \cdot CMe_2 \cdot CO \cdot CH_3 \longrightarrow 2\,CH_3 \cdot CO \cdot CHMe_2 + NH_2 \cdot NH_2$$
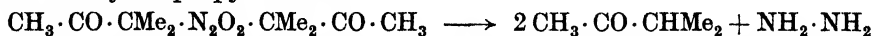
[1] Goldschmidt and Christmann, loc. cit.   [2] L. Pauling, J. Amer. C.S. 1931, 53, 3225.
[3] E. B. Wilson, ibid. 1934, 56, 747.
[4] J. G. Aston, D. F. Menard, and M. G. Mayberry, ibid. 1932, 54, 1530.

The formation of a product containing linked nitrogen atoms strongly suggests that the nitrogen atoms are linked in the bisnitroso group. But there is still further evidence; if the reduction is stopped before it is completed, an intermediate compound can be isolated which has the composition and molecular weight of the azoxy compound,

$$CH_3 \cdot CO \cdot CMe_2 \cdot NO : N \cdot CMe_2 \cdot CO \cdot CH_3.$$
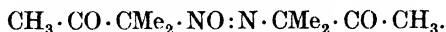
A similar intermediate product is formed in the reduction of the bisnitroso ester, $EtO_2C \cdot CMe_2 \cdot N_2O_2 \cdot CMe_2 \cdot CO_2Et$, under the same conditions;[1] this also appears to be an azoxy compound, and this view finds support in the fact that the same compound can be obtained by oxidizing the corresponding azo-ester, $EtO_2C \cdot CMe_2 \cdot N : N \cdot CMe_2 \cdot CO_2Et$, about whose structure there is no doubt. Hence it seems definite that the nitrogen atoms are linked together in the bisnitroso compound. An objection can be raised against this argument: it is possible that the monomolecular compound is reduced to the hydroxylamine and that the azoxy compound is formed by the well-known condensation of the hydroxylamine and the unchanged nitroso compound (see p. 427) and does not come from the bisnitroso compound at all. This objection carries little weight: the reduction takes place in strongly acid solution and, as we know from the detailed study of the formation of azoxy compounds in the reduction of nitro compounds, the condensation of nitroso compound and hydroxylamine takes place readily only in alkaline solution. The behaviour of bis-nitrosophenyl-methane, $\phi \cdot CH_2 \cdot N_2O_2 \cdot CH_2 \cdot \phi$ (see p. 212), where again there is no tendency to dissociation, supports the same conclusion. If it is treated with hydrogen chloride in chloroform solution, it is converted into a mixture of benzoyl hydrazine $\phi \cdot CO \cdot NH \cdot NH_2$, and its benzylidene derivative $\phi \cdot CO \cdot NH \cdot N : CH \cdot \phi$, both of which contain linked nitrogen atoms.

If this point is taken as established, the structure (I), which has had several supporters,[2] can be excluded. Possible formulae containing linked nitrogen atoms are shown in the formulae (II) and (III), both of which
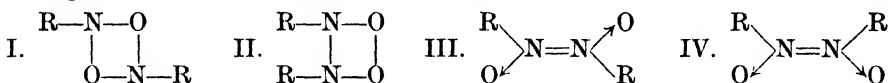
might be reduced to an azoxy compound. Objections can be raised against both these formulae: (II) implies a peroxide linking between the two oxygen atoms, and there is no hint of peroxidic properties in the bisnitroso compounds. There are two objections to structure (III). The first arises from the study of the orienting effect of the nitroso group in benzene substitution. The monomolecular nitroso group would be expected to be meta-directing, both by analogy with the nitro group, by applying Sutton's rule of the connexion between the electric moment of a group in aliphatic and aromatic compounds,[3] and by the other rules of

[1] J. G. Aston and G. T. Parker, *J. Amer. C. S.* 1934, **56**, 1387.

[2] Cf. C. K. Ingold and H. A. Piggott, *J.C.S.* 1924, **125**, 168.

[3] *Proc. Roy. Soc.* 1931, **133**, 668; D. Ll. Hammick, R. G. A. New, and L. E. Sutton, *J.C.S.* 1932, 742.

substitution. The point is difficult to settle directly because the nitroso group in nitrosobenzene is so unstable that it is destroyed in substitution reactions, but that the conclusion is correct is shown by the fact that in o- and p-, but not m-bromo-nitroso-benzene the bromine is readily removed by hydrolysis.[1] This implies that the nitroso group has the same effect as the nitro group (see p. 258) and is meta-directing. C. K. Ingold[2] and R. J. W. Le Fèvre[3] have shown, however, that nitrosobenzene in carbon disulphide and benzene can be rapidly nitrated and brominated in the position para to the nitroso group. These products might, however, be the substitution products of the bimolecular form of nitrosobenzene which is present in small concentration and is rapidly attacked, ortho-para-substitution being in general much faster than meta-substitution. This explanation is confirmed by the fact that in acetic acid, where the nitroso-benzene is wholly monomolecular, bromination is very slow and yields no bromo-nitroso derivative at all, but a complex mixture of brominated azoxybenzenes.[4] The bisnitroso group has thus an ortho-para-directing effect. This can hardly be the case if its structure is (III), because in this the nitrogen atoms are in much the same state of combination as in the

nitro group, $R \cdot N{\overset{\textstyle O}{\underset{\textstyle O}{\diagup}}}$ and must direct to the meta position.

The second objection to structure (III) comes from the estimate which has been made of the electric moment of two bisnitroso compounds.[5] 2-Nitroso-2,5-dimethylhexane dissolves in cold carbon tetrachloride to give a colourless solution which slowly turns blue on standing; by measuring the polarization at intervals and extrapolating back to zero time the electric moment of the bimolecular form was found to be $0\cdot99 \pm 0\cdot10$ D. The second case was nitroso-mesitylene (fourth formula, p. 207) which exists very largely as a bisnitroso compound in benzene: the amount of the monomeric form is known, its contribution to the polarization can be estimated, and thus the electric moment of the bimolecular form was found to be $1\cdot37 \pm 0\cdot13$ D at 8°. Structure (III), however, has a centre of symmetry and presumably must have zero moment. Since it contains doubly bound nitrogen atoms, it might exist in the geometrically isomeric form (IV), but this is almost certainly less stable than (III), and because the compound is being formed and reformed by the association and dissociation, it seems hardly likely that the cis-form (IV) would exist. The cis-form of the azo compounds (p.437) is unknown.

For both these reasons the structure (III) must be rejected. No other structure can be proposed which has any kind of probability. We are thus left with two alternatives between which a decision is impossible until further evidence is available. The first of these is the four-membered ring structure (II), which was suggested by Wieland. Several facts can be advanced in support of this formula. It has no centre of symmetry and

[1] D. Ll. Hammick and W. S. Illingworth, *J.C.S.* 1930, 2358.

[2] Ibid. 1925, **127**, 513.   [3] Ibid. 1931, 810.   [4] Hammick, ibid. 1931, 3105.

[5] Hammick, R. G. A. New, and R. B. Williams, ibid. 1934, 29.

thus will have a finite electric moment, although it is difficult to say from the formula what the moment will be; it contains trivalent nitrogen and thus almost certainly there will be an ortho-para-directing effect in the aromatic compounds. Moreover, other cases of polymerization to four-membered rings have been established with certainty, as in the ketenes which polymerize as shown:

$$2\,R_2C\!:\!CO \longrightarrow \begin{array}{c} R_2C\!\!-\!\!CO \\ | \quad\;\; | \\ OC\!\!-\!\!CR_2 \end{array}$$

In this connexion it is interesting to remember that the nitroso compounds combine with ketenes to give four-membered rings (see p. 210).

The second alternative is a modification of structure (III).[1] It has been suggested that the electrons which form the links between the atoms might assume the two arrangements different from that implied in (III) which are shown in (V).

V. $\begin{array}{c} R \\ \diagdown \\ O \diagup \end{array}\!\!N\!\leftarrow\!N\!\begin{array}{c} \diagup O \\ \diagdown R \end{array}$ $\begin{array}{c} R \\ \diagdown \\ O \diagup \end{array}\!\!N\!\rightarrow\!N\!\begin{array}{c} \diagup O \\ \diagdown R \end{array}$ III. $\begin{array}{c} R \\ \diagdown \\ O \diagup \end{array}\!\!N\!\!=\!\!N\!\begin{array}{c} \diagup O \\ \diagdown R \end{array}$
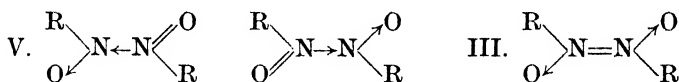
If now all these three arrangements (III and V) are of approximately equal energy, the actual state of the molecule might be that of a resonance-hybrid to which the three forms contribute. This would give some reason for the electric moment, since the unsymmetrical structures (V) contribute to the resonance-hybrid, and possibly for the orientation in substitution. The difficulty of such a view is that it suggests that a bisnitroso compound should be formed in the oxidation of an azoxy compound, just as an azoxy compound can be obtained by oxidizing an azo compound. Until more evidence is available, the structure of the bisnitroso compounds must be left as an incompletely solved problem.

Nitrosoanilines

The o- and p-amino-nitrosobenzenes and their derivatives can be prepared by special methods and differ in many respects from the compounds described so far. The primary and secondary amino compounds (e.g. VI) behave in some ways as though they were monoximes of quinone-mono-imines (e.g. VII), and tautomerism between the two structures has often been postulated. Since, however, some of their peculiarities are shown also by the tertiary amino compounds, in which tautomerism of this kind

NO	NOH	NO⁻	NO	NO
NH₂	NH	NR₂⁺	NHMe	NMe₂
VI.	VII.	VIII.	IX.	X.
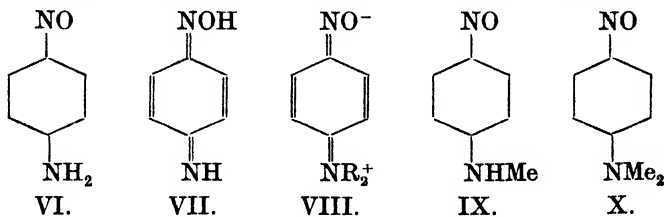
[1] D. Ll. Hammick, *J.C.S.* 1931, 3105.

is impossible because there is no hydrogen atom attached to the amino nitrogen, there is the further possibility that the compounds can assume the internal-salt (zwitterion) structure (VIII). The substances with the substituents in the para position are the best known, and these alone will be discussed. *p*-Nitrosoaniline (benzoquinone imine oxime, VI and VII) is obtained from *p*-nitrosophenol (a compound which is tautomeric with quinone monoxime and is discussed below) by melting it on the water bath with a mixture of the chloride, acetate, and carbonate of ammonium. It forms steel-blue needles, and is oxidized smoothly by permanganate to *p*-nitraniline, and reduced to *p*-phenylene diamine. It gives salts both with acids and bases. The former might be derived from the true nitroso compound (VI), but they are yellow solids and are yellow in solution and thus do not seem to contain the true nitroso group. A striking reaction of the compound is its hydrolysis by alkalis to quinone monoxime (*p*-nitrosophenol) and ammonia. This peculiar and important reaction is discussed more fully below.

$$ON\langle\bigcirc\rangle NH_2 + NaOH \longrightarrow ON\langle\bigcirc\rangle ONa + NH_3$$
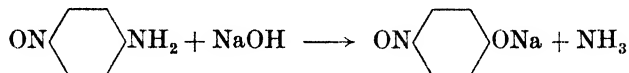
Similar properties are shown by *p*-nitrosomethylaniline (IX). This is readily obtained by allowing methylphenylnitrosamine, $\phi \cdot N\langle^{Me}_{NO}$, to stand with alcoholic hydrogen chloride, when the hydrochloride of (IX) slowly crystallizes; the nitroso group appears to migrate from the nitrogen atom to the para position (see p. 452). This compound also is steel-blue in the solid state, forms sandy-yellow salts with acids, and is soluble in aqueous caustic soda. It behaves as though it contained a secondary amino group, as in (IX), in that it gives with nitrous acid the nitrosonitrosamine, $NO \cdot C_6H_4 \cdot N(CH_3)NO$; it is hydrolysed by hot alkali to methylamine and quinone monoxime.

The tertiary amino compounds of this group are the best known, and are formed with great ease by the action of nitrous acid on most tertiary aromatic amines (see p. 60). The mechanism of the reaction is by no means simple: the product certainly contains the nitroso group attached to the ring in the para position, since it can be reduced to a derivative of *p*-phenylene-diamine, but the tertiary amino group is involved in the first stages of the reaction. This is shown by the fact that if the alkyl groups in the amino group are large, as in di-isoamylaniline, the reaction fails completely; and also that if groups are present in the ortho position to the amino group, as in *o*-chloro- (or methyl-) dimethylaniline, steric hindrance comes into play and the reaction takes place with great difficulty.[1] It is clear that in the first stage there is an addition complex between the tertiary amino group and nitrous acid, whose formation can be hindered by ordinary steric effects, and that this complex ultimately rearranges to

[1] P. Karrer, *Ber.* 1915, **48**, 1398.

the p-nitroso compound. The preparation of p-nitrosodimethylaniline is carried out in a manner somewhat similar to the diazotization of a primary aromatic amine; hydrochloric acid is generally used to dissolve the amine and the hydrochloride of the nitroso compound crystallizes out. The free base forms grass-green crystals and is the best known of all nitroso compounds. It is known commercially as 'nitroso base M', and is of technical importance as a dye-stuff intermediate, especially for the manufacture of thiazine dyes such as methylene blue, because of the ease with which it is reduced to p-aminodimethylaniline. p-Nitrosodimethylaniline shows many of the characteristics of a true nitroso compound: it is oxidized to p-nitrodimethylaniline and the ease with which it condenses with compounds containing a reactive methylene group has led to its use as a reagent for such groups. It shows the typical green colour of an aromatic nitroso compound and in solution is associated to an extent of about 20 per cent. The green colour of the solid indicates that the bisnitroso form does not exist in the crystal, and the green colour of its solution in toluene persists even if it is cooled to —100°. On the other hand, its salts with acids are yellow and not green, so that as a cation it does not seem to contain a true nitroso group. Like p-nitrosoaniline and the corresponding monomethylaniline, it is hydrolysed by alkalis, and gives quinone monoxime and dimethylamine.

The question of the structure of the nitrosoanilines involves three separate points. The first, the structure of the primary and secondary amines as anions in their sodium salts, admits of little doubt: it must be derived from the quinone imine oxime structure (VII). The structure of all three compounds as kations in their salts with acids is not so definite, but the balance of the evidence seems again to indicate a quinone structure (XI) rather than the ammonium salt (XII); in addition to the disappearance of the typical nitroso-absorption spectrum on salt formation, the
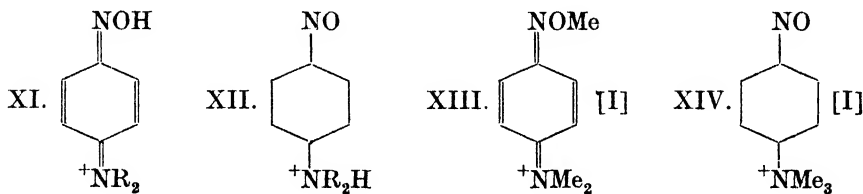
action of alkyl halides on the compounds is of importance. The distinction between (XI) and (XII) is the position taken up by the entering proton when the kation is formed; this cannot be proved simply, but if methyl iodide is substituted for hydrogen chloride, the methyl group will most probably take up the same position as the proton and that position can be established. The two alternative formulae for the methiodide of nitrosodimethylaniline are (XIII) and (XIV), and of these the latter is ruled out by the fact that the compound on hydrolysis gives dimethylamine and not trimethylamine.[1] The third point is the structure of the

free bases. Since primary, secondary, and tertiary compounds show so many points of resemblance, it seems difficult to explain the behaviour of the first two classes by postulating a true tautomerism between structures (VI) and (VII), since in the tertiary compounds this is impossible. A more likely suggestion is that all three classes may exist in the zwitterion form (XV), from which the anion and kation can easily be derived. Important

$$\overset{+}{HNR}=\hspace{-4pt}\left\langle\underset{\underline{\hspace{18pt}}}{\overline{\hspace{18pt}}}\right\rangle\hspace{-4pt}=NOH \quad\xleftarrow{\ H^+\ }\quad \overset{+}{HNR}=\hspace{-4pt}\left\langle\underset{\underline{\hspace{18pt}}}{\overline{\hspace{18pt}}}\right\rangle\hspace{-4pt}=NO^-$$

XV.

$$\xrightarrow{\ OH^-\ } \quad RN=\hspace{-4pt}\left\langle\underset{\underline{\hspace{18pt}}}{\overline{\hspace{18pt}}}\right\rangle\hspace{-4pt}=NO^- + H_2O$$
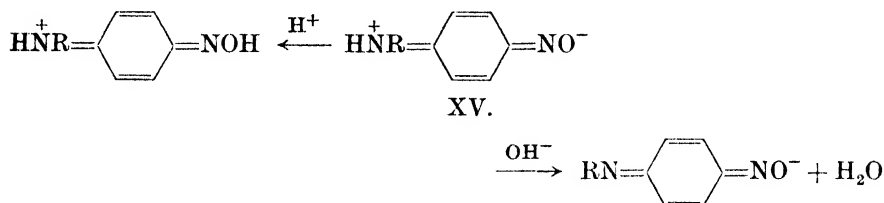
evidence is given by the abnormally high values of the electric moments of the compounds.[2] With the great majority of p-di-substituted benzene derivatives the electric moment of the molecule is very nearly the vectorial sum of the moments of the two substituting groups: this is not the case with these compounds (moment of $\phi\cdot NO$ is 3·14 D, of $\phi\cdot NHMe$, 1·64 D, and of $\phi\cdot NMe_2$, 1·58 D).

| | Electric moment in | | Sum of |
	Benzene	CCl_4	moments
$ON\cdot C_6H_4\cdot NHMe$ . . .	7·38	..	4·78
$ON\cdot C_6H_4\cdot NMe_2$ . . .	6·89	6·33	4·72
$ON\cdot C_6H_4\cdot NEt_2$ . . .	7·18	6·90	..

These results show that the compounds cannot exist entirely as zwitterions, whose moment would be much larger (of the order of 30 D): this is also indicated by the properties, since true zwitterions, e.g. the aliphatic amino-acids, are quite insoluble in benzene. The high values, however, indicate that in solution there is some tendency to assume the polar form (XV). Now the zwitterion form (XV) and the normal benzenoid form (IX) are interconvertible simply by the movement of electrons and without the shifting of any atom, so that resonance may well take place between the two. Hence the most probable structure of the free bases is that of a resonance-hybrid of the two forms. Which of the two component structures predominates in the hybrid may vary with conditions such as solvent and temperature.

The action of aqueous alkalis on nitrosoanilines, both the unsubstituted and the alkylated compounds, has been mentioned already. In all cases hydrolysis takes place with the formation of the salt of a quinone monoxime and an amine. This reaction, which at first sight is somewhat abnormal, is a good illustration of the attack of a negative ion (an anionoid reagent)

[1] L. Knorr, *Ber.* 1897, **30**, 933.

[2] R. J. W. Le Fèvre and J. W. Smith, *J.C.S.* 1932, 2239.

on the positively charged part of a molecule (the kationoid centre, where there is a deficit of electrons). It can be represented in the following way:

$$\bar{O}N=\hspace{-0.3em}\langle\hspace{1em}\rangle\hspace{-0.3em}=\overset{+}{N}Me_2 + OH^- \longrightarrow \bar{O}N=\hspace{-0.3em}\langle\hspace{1em}\rangle\hspace{-0.3em}=O + NHMe_2.$$
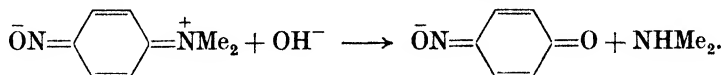
The reaction is of considerable value for preparative purposes, and the following are some examples to which it has been applied.

(a) Pure dimethylamine, free from methylamine and trimethylamine, can be prepared by the hydrolysis of p-nitroso-dimethylaniline.

(b) The heterocyclic compound piperazine is only formed in bad yield by the action of ammonia on ethylene dibromide. If, however, ethylene dibromide and aniline are heated to 140° with some sodium acetate or carbonate, an excellent yield of N,N'-diphenyl-piperazine is obtained.

$$\phi NH_2 + \begin{array}{c} Br \cdot CH_2 \cdot CH_2 \cdot Br \\ Br \cdot CH_2 \cdot CH_2 \cdot Br \end{array} + H_2N\phi \longrightarrow \phi N\hspace{-0.3em}\begin{array}{c} CH_2-CH_2 \\ CH_2-CH_2 \end{array}\hspace{-0.3em}N\phi$$
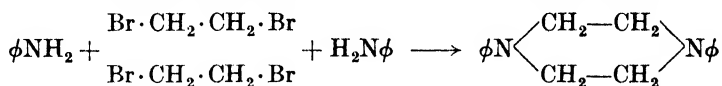
This compound contains two tertiary aromatic amino groups, so with nitrous acid it gives a dinitroso derivative, which can be hydrolysed to piperazine in good yield.

$$ON\hspace{-0.3em}\langle\hspace{1em}\rangle\hspace{-0.3em}-N\hspace{-0.3em}\begin{array}{c} CH_2-CH_2 \\ CH_2-CH_2 \end{array}\hspace{-0.3em}N-\hspace{-0.3em}\langle\hspace{1em}\rangle\hspace{-0.3em}NO$$

$$\longrightarrow HN\hspace{-0.3em}\begin{array}{c} CH_2-CH_2 \\ CH_2-CH_2 \end{array}\hspace{-0.3em}NH + 2ON \cdot C_6H_4 \cdot OH.$$
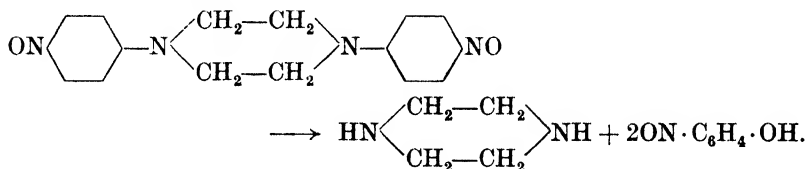
(c) A further application is to the preparation of monoalkyl aliphatic diamines. A chloro- (or bromo-) alkylamine is condensed with a mono-alkylaniline; the product is dissolved in hydrochloric acid and sodium nitrite added, when a p-nitroso compound is formed, the nitrous acid only reacting slowly with the primary amino group in the presence of the mineral acid (see p. 24). Alkaline hydrolysis then gives the desired product.

$$NH_2 \cdot CH_2 \cdot CH_2Cl + HNEt\phi \longrightarrow NH_2 \cdot CH_2 \cdot CH_2 \cdot NEt\phi$$

$$\downarrow$$

$$NH_2 \cdot CH_2 \cdot CH_2 \cdot NHEt + HO \cdot C_6H_4 \cdot NO \longleftarrow NH_2 \cdot CH_2 \cdot CH_2 \cdot NEt\hspace{-0.3em}-\hspace{-0.3em}\langle\hspace{1em}\rangle\hspace{-0.3em}-NO$$
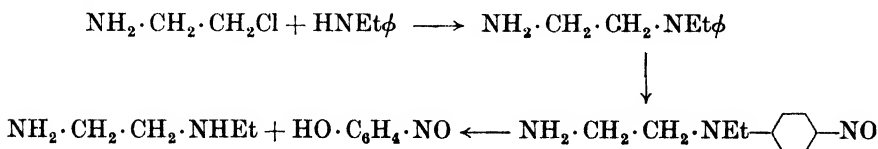
Nitrosophenols or Quinone Monoximes

When phenol reacts with nitrous acid, a compound is formed which is identical with that obtained by the action of one equivalent of hydroxyl-amine on benzoquinone:

$$\langle\hspace{1em}\rangle\hspace{-0.3em}-OH \longrightarrow ON\hspace{-0.3em}\langle\hspace{1em}\rangle\hspace{-0.3em}OH \rightleftharpoons HON=\hspace{-0.3em}\langle\hspace{1em}\rangle\hspace{-0.3em}=O \longleftarrow O=\hspace{-0.3em}\langle\hspace{1em}\rangle\hspace{-0.3em}=O$$

$$\text{I.} \hspace{8em} \text{II.}$$
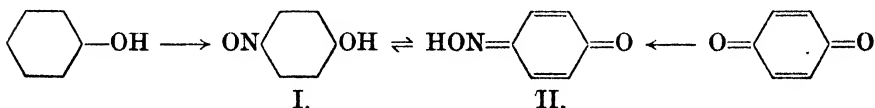
It melts with decomposition at about 125° and can be obtained in two crystalline forms, the one almost colourless by recrystallization from water, and the other yellowish green from acetone. Both give identical solutions, which in water, alcohol, and ether are green, and in benzene and chloroform are yellow. In ether it is monomolecular, and in benzene the molecular weight is one and a half times that required by the simple formula. The substance is oxidized to p-nitrophenol and reduced to p-aminophenol. It is by no means easy to determine the structure of this and similar compounds. It forms a well-defined sodium salt which could clearly be derived from either of the possible formulae (I) and (II). The most important piece of evidence, showing that in solution it exists as a tautomeric mixture of the two, comes from a study of its methylation products.[1] Quinone monoxime (II) would be expected to give its methyl ether, $MeON:C_6H_4:O$, a known compound formed by the action of O-methylhydroxylamine on quinone, and this is indeed formed by the action of both diazomethane and methyl iodide and alkali on the compound. In addition, however, another compound is obtained which has been shown to be the N-hydroxyphenyl ether of glyoxime (III) together with a certain amount of the N-methoxyphenyl ether, presumably resulting from further methylation.

$$HO-\langle\!\!\!\bigcirc\!\!\!\rangle-\overset{\overset{O}{\uparrow}}{N}:CH\cdot CH:\overset{\overset{O}{\uparrow}}{N}-\langle\!\!\!\bigcirc\!\!\!\rangle-OH$$

III.
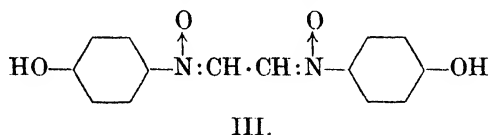
Now it is known that when nitrosobenzene is treated with diazomethane, a very curious reaction takes place and di-N-phenyl-glyoxime is produced; since some nitrosobenzene always undergoes reduction during the reaction, its probable course is as follows, the diazomethane first adding on to the double bond as in many similar reactions:

$$\phi\cdot NO + CH_2N_2 \longrightarrow \begin{array}{c}\phi\cdot N\!\!-\!\!O \\ | \qquad\quad \rangle\!N \\ CH_2\!\!-\!\!N\!\!\nearrow\end{array} \longrightarrow \begin{array}{c}\phi\cdot N\!\!-\!\!O\!\!- \\ | \\ CH_2\!\!-\end{array} \xrightarrow{\text{oxidation}} \left(\begin{array}{c}\phi\cdot N\!\!\rightarrow\!\!O \\ \| \\ CH\!\!-\end{array}\right)_2$$
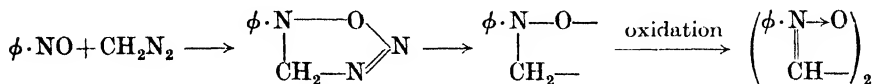
Hence this seems to be definite evidence that a true nitroso compound is present in a solution of p-nitrosophenol. This evidence, of course, tells us nothing of the proportions in which the two forms are present, because the amounts of the two products formed depend, not only on the amounts of the two forms, but on the relative speeds with which they react with the methylating agents, and these are unknown. Evidence from a physical source, however, indicates that p-nitrosophenol is very largely present in the quinone monoxime form. If the light absorption of solutions of the compound in dioxane, chloroform, alcohol, and dilute aqueous acids is compared with that of the methyl derivatives of the two possible forms

[1] H. von Pechmann, *Ber.* 1897, **30**, 2871; von Pechmann and E. Seel, ibid. 1898, **31**, 296; H. H. Hodgson, *J.C.S.* 1932, 1395.

(p-nitrosoanisole, $ON.C_6H_4 \cdot OMe$, can be obtained by oxidizing p-methoxy-aniline with Caro's acid), there is a very strong resemblance between that of quinone monoxime O-methyl ether and that of the compound, but no similarity to that of p-nitrosoanisole.[1]

In a few cases it has been stated that it is possible to obtain the two tautomeric forms of a nitrosophenol as separate pure solids. An example is afforded by one of the products of the action of nitrous acid on the monoethyl ether of resorcinol.[2] This can be obtained by recrystallization from benzene as green leaflets, which at 130° pass into a yellow compound melting at 147–148°. The yellow substance is also obtained by recrystallization from alcohol or acetone. Both forms give the same sodium salt, and with phenyl isocyanate the same urethane. It may well be that the green substance is the nitroso compound (IV) and the yellow the quinone monoxime (V). The apparent conversion of one solid tautomer into the
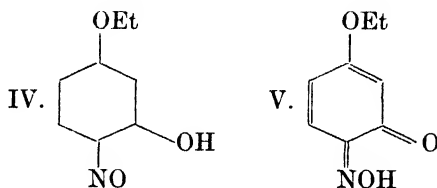
other by recrystallization and vice versa is curious, since in general the relative stability of the two solids must be independent of the solvent in contact with them. When it is found that solvents can convert either form into the other, this may usually be taken to mean that the unstable form separates from one solvent, in which it is present in large amount, before it has time to change into the stable form.

A similar case is that of 3-chloro-4-nitrosophenol.[3] The first product isolated from the action of nitrous acid on m-chlorophenol melts at 133° and is rapidly converted by both acids and alkalis into another (m.p. 184°): the first compound on methylation gives a mixture of the two products which are derived from the nitrosophenol and quinone monoxime structures, but the isomeric compound is methylated entirely to the quinone monoxime methyl ether. These facts would again appear to indicate the separate existence of the two tautomers, although there are unsolved difficulties in the absorption spectra of the two compounds.[4]

In the case of β-naphthol, the para position to the hydroxyl group is blocked so that in the reaction with nitrous acid, the nitroso group enters the reactive α-position. The product, whether it is a nitrosophenol (VI) or the monoxime of an orthoquinone (VII), contains a hydroxyl group and a doubly bound oxygen atom in proximity, and thus forms metallic

[1] L. C. Anderson and M. B. Geiger, *J. Amer. C. S.* 1932, 54, 3064; Anderson and R. L. Yanke, ibid. 1934, 56, 732.

[2] F. Henrich, *J. pr. Chem.* 1904, 70, 313.

[3] H. H. Hodgson and A. Kershaw, *J.C.S.* 1929, 1553.

[4] Anderson and Yanke, loc. cit.

derivatives which have a chelate structure; this may be written in either of the two ways (VIII) and (IX), which represent the cobalt derivative of nitroso-β-naphthol. The complex contains three nitrosonaphthol residues united to one cobalt atom, and only one of these residues is shown in full.

VI.

VII.

VIII.

IX.
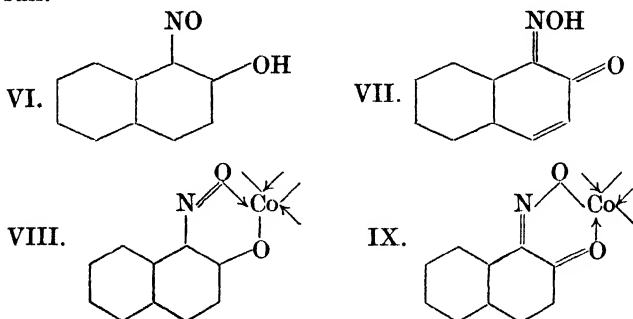
The actual structure of these complexes is almost certainly that of a resonance-hybrid of these two formulae. The same type of metallic complex is formed by all nitrosophenols in which the hydroxyl group is in the ortho position to the nitroso group. The metallic complexes are interesting from two points of view. Firstly the cobaltic complex of nitroso-β-naphthol is formed readily in the presence of dilute acids and is insoluble in water, while the nickel complex is decomposed by acids. Hence nitroso-β-naphthol is frequently used as an analytical reagent, both for the detection and the estimation of cobalt in the presence of nickel. Secondly, some of the metallic complexes are deeply coloured and can combine with textile fabrics. They are thus of some commercial value as mordant dye-stuffs, and form the group known as the nitroso dyes. The fabric is first treated with a solution of an easily hydrolysed salt of the metal (mordanted), and then dyed in a bath of the dye-stuff. Nitrosonaphthol itself gives a bright fast green on an iron mordant and is known as Steam Green. Naphthol Green B is also used with an iron mordant for dyeing wool; it is prepared by the action of nitrous acid on 2-naphthol-6-sulphonic acid (Schaeffer's acid) and has the structure (X).

X.

XI.
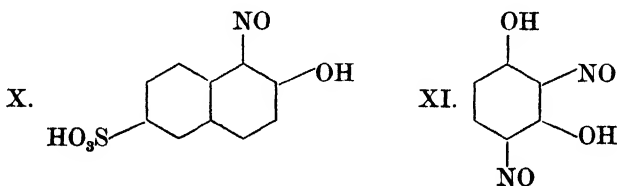
When resorcinol is treated with nitrous acid in dilute mineral acid, 2,4-dinitroso-resorcinol (XI) is obtained.[1] This compound is known as

[1] Direct di-substitution of resorcinol usually gives the 4,6 and not the 2,4-substitution product; the reasons underlying the abnormal formation of a 2,4 derivative in the case mentioned above are discussed by W. Baker, *J.C.S.* 1934, 1684.

Resorcin Green or Solid Green O; it gives a very fast green on iron-mordanted fabrics and a brown on chromium mordants.

The Addition of Oxides of Nitrogen to Ethylenic Compounds

We may consider briefly a rather confusing group of substances formed by the addition of nitrosyl chloride, nitrogen trioxide, N_2O_3, and nitrogen peroxide, N_2O_4, to the double bond of ethylenic compounds. The most important substances of this group are the derivatives of the terpenes, which are naturally occurring unsaturated hydrocarbons. In order to separate individual compounds from the complicated mixtures in which they occur, the products obtained by the addition of various reagents were studied, and in this way the nitrosochlorides, nitrosites, and nitrosates were obtained and their properties investigated.[1] Confusion arises in this subject because the structures which were accepted for some of the compounds are now known to be erroneous and certain generalizations which were thought to hold in their reactions have been disproved. The main interest of these compounds lies not in their properties and reactions, but in their application to the separation and identification of certain terpenes. The usual way in which they are prepared is to pass 'nitrous fumes' (e.g. from arsenious oxide and nitric acid) into the hydrocarbon with or without a solvent. The products are formed by the addition to the hydrocarbon of nitrogen trioxide, nitrogen peroxide, or sometimes of nitric acid, which is formed from the peroxide and the traces of water present. If hydrochloric acid is added, the addition of nitrosyl chloride often takes place. Other conditions of reaction are sometimes used: for example, the unsaturated compound may be dissolved in glacial acetic acid and sodium nitrite added, either in the solid state or in concentrated aqueous solution, or a mixture of the unsaturated compound and amyl nitrite may be treated with concentrated hydrochloric acid.

The addition seems to take place most easily with compounds of the formula $RR'C:CHR''$, though it is not restricted to these.

Those products which contain the nitroso group almost always occur in the bimolecular (bisnitroso) form in the solid state and sometimes in solution. The principal types of compound which have been obtained possess the following structures:

I. $\left(\begin{array}{cc} -CH-C\langle \\ | \quad | \\ NO \quad Cl \end{array}\right)_2$ Nitrosochloride

II. $\left(\begin{array}{cc} -CH-C\langle \\ | \quad | \\ NO \quad NO_2 \end{array}\right)_2$ Nitrosites and pseudo-nitrosites

III. $\left(\begin{array}{cc} -CH-C\langle \\ | \quad | \\ NO \quad O \cdot NO_2 \end{array}\right)_2$ Nitrosates

IV. $\begin{array}{cc} \rangle C-C\langle \\ | \quad | \\ NO_2 \quad NO_2 \end{array}$ The so-called 'Dinitrüre'

V. $\begin{array}{cc} -C\!-\!-C\langle \\ \| \quad | \\ NOH \quad NHR \end{array}$ Nitrolamines

VI. $\begin{array}{cc} -C\!-\!-C\langle \\ \| \quad | \\ NOH \quad NO_2 \end{array}$
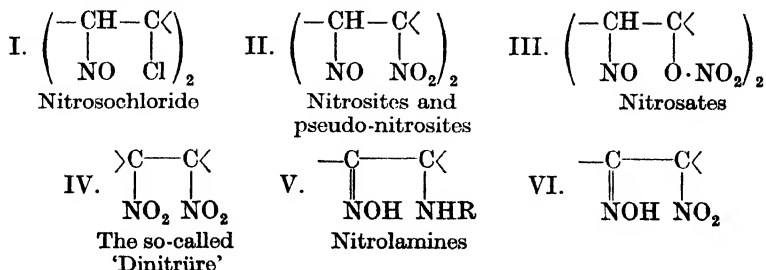
[1] See L. Ruzicka, Pedler Lecture on the Life of Otto Wallach, *J.C.S.* 1932, 1582, and O. Wallach, *Terpene und Campher*, 2nd ed. Leipzig, 1914, p. 69 et seq.

The type formed in any given case depends on the conditions and the nature of the groups in the molecule. The nitrosochlorides obviously arise from ..ddition of NOCl, the nitrosites from that of N_2O_3, and the two last groups from N_2O_4. The two last groups will not be discussed here: the 'Dinitrüre' are mentioned later (p. 244) and the structure of the nitrosates presents certain unsolved difficulties. For many years the second group was subdivided into two, the pseudo-nitrosites which were thought to possess structure (II) and the nitrosites in which the NO_2 group was thought to be a nitrous ester group $\geqslant C \cdot O \cdot NO$. All compounds of this class, however, are reduced to diamines, so that in all cases both nitrogen atoms must be attached to carbon.[1]

With ammonia and primary and secondary amines both nitroso-chlorides and nitrosites give nitrolamines which usually crystallize well and are useful for identification. These compounds have the structure (V) and are formed by the replacement of the chlorine atom or nitro group, followed by the normal nitroso $\longrightarrow$ oximino change which would be expected to occur in the presence of an alkali. The nitrosites of structure $R \cdot CHNO \cdot CHRNO_2$ are converted into nitro-olefines by alcoholic potash or concentrated sulphuric acid, hyponitrous acid being split off and appearing as nitrous oxide.

$$\begin{array}{c} RCH \cdot CHR' \cdot NO_2 \\ | \\ N_2O_2 \\ | \\ RCH \cdot CHR' \cdot NO_2 \end{array} \longrightarrow \begin{array}{c} RCH : CR' \cdot NO_2 \\ \\ RCH : CR' \cdot NO_2 \end{array} + N_2O + H_2O$$
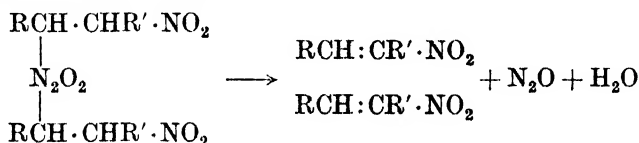
All nitrosites of formula (II) on boiling with alcohol, water, or dilute acids undergo the normal change to nitro-oximes (VI).[2] If there is a hydrogen atom attached to the carbon atom which carries the nitro group, the reagents convert the compound into a so-called 'glyoxime peroxide', which is really a furazane oxide (VII: see p. 345).[3] This takes place through the intermediate formation of the aci-form of the nitro group, followed by loss of water.[4]

$$\begin{array}{cc} R \cdot CH\text{---}CHR' \\ | \quad\quad | \\ NO \quad NO_2 \end{array} \longrightarrow \begin{array}{cc} R \cdot C\text{----}CHR' \\ \| \quad\quad | \\ NOH \quad NO_2 \end{array}$$

$$\longrightarrow \begin{array}{cc} R \cdot C\text{-------}C \cdot R' \\ \| \quad\quad\quad | \\ NOH \quad HO \cdot N{\to}O \end{array} \longrightarrow \begin{array}{cc} R \cdot C\text{-----}C \cdot R' \\ \| \quad\quad\quad \| \\ N \quad\quad N{\to}O \\ \diagdown \;\; \diagup \\ O \end{array}$$

VII.
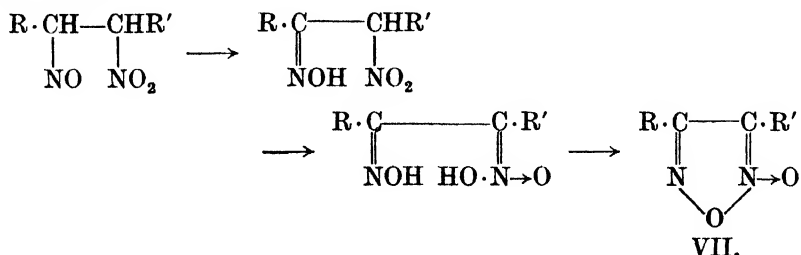
[1] H. Wieland, *Annalen*, 1921, **424**, 71.   [2] H. Wieland, ibid. 1903, **329**, 225.
[3] A. Angeli, *Gazz.* 1902, **32**, ii. 132.   [4] H. Wieland, *Annalen*, 1921, **424**, 107.

NITRO COMPOUNDS

THE nitro compounds contain the group —NO_2. That this group is attached to carbon by means of the nitrogen atom is shown by the fact that the compounds can be reduced to primary amines:

$$C \cdot NO_2 \longrightarrow C \cdot NH_2.$$
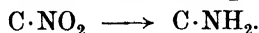
The structure has been written in three ways.

$$\text{I. } C\!-\!N\!\!\diagdown\!\!\genfrac{}{}{0pt}{}{O}{O} \qquad \text{II. } C\!-\!N\!\!\diagdown\!\!\genfrac{}{}{0pt}{}{O}{O} \qquad \text{III. } C\!-\!N\!\!\diagdown\!\!\genfrac{}{}{0pt}{}{O}{O}$$
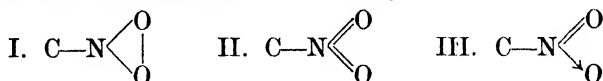
The first of these has long been abandoned; it offers no explanation for the similarity between the tautomerism of the group —$CH_2 \cdot NO_2$ and that of the keto grouping —$CH_2 \cdot CO$—; further, such a stable group as the nitro group is unlikely to contain a three-membered ring, for when the latter occurs it can usually be opened easily and thus shows unsaturated properties to some extent. The second and third formulae differ in the type of linking they imply between the nitrogen atom and the oxygen atoms; in the former there are two true double bonds between nitrogen and oxygen, the nitrogen atom is pentacovalent and is surrounded by ten valency electrons; in the latter there is one true double bond and one bond formed by two electrons from the nitrogen atom, a co-ordinate link, and the nitrogen is tetracovalent with eight valency electrons. Since compounds containing nitrogen united to five groups by covalencies are unknown (e.g. NMe_5), the third formula is to be preferred.

This formula does not, however, imply any discernible difference between the two oxygen atoms, any more than there is any difference between the oxygen atoms in the carboxylate ion —$C\!\diagdown\!\genfrac{}{}{0pt}{}{O^-}{O}$, or the nitrogen atoms in the amidine ion —$C\!\diagdown\!\genfrac{}{}{0pt}{}{NH_2}{NH_2^+}$. The absence of such a difference is clearly shown by the observed values of the molecular electric moment of a compound such as p-dinitrobenzene. This compound in solution has a very small moment,[1] like p-dichlorobenzene and unlike quinol dimethylether or tetramethyl p-phenylenediamine.

$$O_2N\!-\!\langle\bigcirc\rangle\!-\!NO_2 \qquad Cl\!-\!\langle\bigcirc\rangle\!-\!Cl \qquad \overset{Me}{\diagdown}O\!-\!\langle\bigcirc\rangle\!-\!O\overset{Me}{\diagup} \qquad Me_2N\!-\!\langle\bigcirc\rangle\!-\!NMe_2$$

$$\mu = 0{\cdot}6 \qquad\qquad \mu = 0{\cdot}3 \qquad\qquad \mu = 1{\cdot}7\ D \qquad\qquad \mu = 1{\cdot}23\ D$$
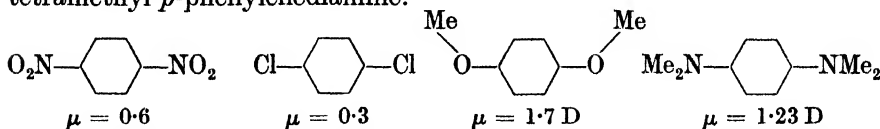
The moments of two para groups oppose one another, and if they lie along the same axis, the total moment is small. If they do not (as in $C\!-\!O\!\diagup^{CH_3}_{CH_3}$ or in $N\!\diagup^{CH_3}_{CH_3}$), the moment is large, because it can only vanish

[1] L. Tiganik, *Z. phys. Chem.* 1931, B, **13**, 425.

if the two groups are held in the *trans* position to one another, when the molecule has a centre of symmetry, and thermal agitation prevents any such uniforn arrangement. Thus, since *p*-dinitrobenzene shows such a small moment, the group $C-N\langle^O_O$ must be symmetrical about the C—N link, and this is impossible if there is any distinction between the oxygen atoms. This identity should not be regarded as apparent and arising from an oscillation of the valency electrons involved, such as might be represented in the scheme $-N\langle^O_O \rightleftharpoons -N\langle^O_O$. It is an actual identity and has its origin in the phenomenon of resonance. When there are two or more states in which a molecule may exist and which possess the same, or very nearly the same, energy content and do not involve any difference in the positions of the constituent atoms or any great difference in the distances between them, then the molecule is a resonance-hybrid; its energy is smaller than that of any of the states from which it derives, and hence its stability is greater; it behaves as though it were a mixture of molecules in the constituent states, but appears to contain more of those of smaller energy content; and finally the distances between its atoms are not the normal ones, but are shorter.

The aromatic nitro compounds differ from the aliphatic in that the former are all necessarily tertiary. Many of the reactions of the primary and secondary aliphatic nitro compounds involve the hydrogen atom or atoms attached to the carbon atom carrying the nitro group, and these, of course, cannot occur with the aromatic compounds. The two classes will therefore be considered separately.

ALIPHATIC NITRO COMPOUNDS

The aliphatic nitro derivatives were not discovered until long after their aromatic analogues were well known. Members of the class were first prepared by Victor Meyer in 1872 and by Kolbe shortly afterwards.

The method of direct nitration is of more restricted application in the aliphatic series than in the aromatic. As regards the paraffins themselves, the most favourable conditions for direct nitration are, in general, the converse of those used for benzene and its homologues; M. Konovalov showed by an exhaustive series of experiments that dilute nitric acid and a high temperature (100–140°) give the best yield. Tertiary paraffins (e.g. Me_3CH) can be nitrated most easily, sometimes in the cold with strong nitric acid, secondary paraffins less easily, and normal paraffins with more difficulty still. The yields are usually better if the reaction mixture is heated in a sealed tube and not in an open vessel. The nitration is always accompanied by a certain amount of oxidation, and it is to avoid excessive oxidation that the acid is diluted. The mechanism of aliphatic nitration is probably fundamentally different from aromatic nitration: for example, the mixture of concentrated nitric and sulphuric acids commonly used in

aromatic nitration is without any action on certain tertiary paraffins at a temperature where nitric acid alone will react readily.[1]

The introduction of negative groups into the paraffins facilitates their direct nitration. Thus Konovalov[2] found that chlorine derivatives of paraffins such as butane and pentane are more easily nitrated than the hydrocarbons themselves. Similarly ethyl acetate and ethyl acetoacetate can be nitrated by pure nitric acid in the presence of acetic anhydride at 30–35° to give from either compound nitroacetic ester;[3] malonic ester is nitrated at room temperature by nitric acid[4] and its amide by somewhat diluted nitric acid at 10°.[5] It is not impossible that the explanation of these latter cases of ready nitration is enolization of the compound nitrated. The enolic forms are unsaturated substances and these are known to add on the elements of nitric acid, as is discussed later; loss of water from the addition complex would lead to the nitro compound.

$$-CO \cdot CH_2- \longrightarrow -C(OH):CH- \longrightarrow -C(OH)_2 \cdot CHNO_2-$$
$$\longrightarrow -CO \cdot CHNO_2-$$
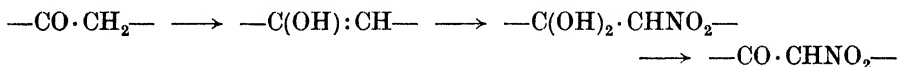
Several methods for the preparation of aliphatic nitro compounds are based on the replacement of a halogen atom or acid radical by the nitro group by means of a metallic nitrite. Victor Meyer's method is to heat an alkyl halide with silver nitrite. In the case of methyl iodide the product is almost entirely nitromethane,

$$CH_3I + AgNO_2 \longrightarrow CH_3 \cdot NO_2 + AgI,$$
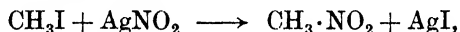
but in all other cases the isomeric alkyl nitrite, $RO \cdot NO$, is formed as well. The proportions in which the nitro compound and the nitrite are obtained varies with the nature of the alkyl group. Primary alkyl halides containing up to three carbon atoms give mainly the nitro compound. Secondary alkyl halides and all halides containing more than four carbon atoms give very small yields of the nitro compound, and tertiary halides give practically none. Silver nitrite can be replaced by the mercurous salt, but other metallic nitrites give no nitro compound with the simple alkyl halides.[6] Nitro-alcohols, nitro-olefines, nitro-ketones, and nitro-acids have been prepared by this method. To obtain phenylnitromethane and its substitution products by this method, the corresponding iodide and silver nitrite must be mixed in dry ether at 0° and left for 24 hours without heating.[7] In this way J. von Braun and O. Kruber[8] prepared the series of compounds of the general formula $\phi \cdot (CH_2)_n \cdot NO_2$ up to the member where $n = 7$, in yields varying between 50 and 70 per cent.

A somewhat similar method for preparing nitromethane and nitro-ethane is the interaction of alkali or alkaline earth nitrites with dimethyl

[1] W. Markovnikov, *Ber.* 1899, **32**, 1444.   [2] *Zent.* 1904, i, 1478.
[3] L. Bouveault and A. Wahl, *Bull. Soc. chim.* 1904, [iii], **31**, 847.
[4] A. P. N. Franchimont and E. A. Klobbie, *Rec. trav. chim.* 1889, **8**, 283.
[5] F. Ratz, *Monats.* 1904, **25**, 58.
[6] F. Kaufler and C. Pomeranz, ibid. 1901, **22**, 492.
[7] A. F. Holleman, *Rec. trav. chim.* 1894, **13**, 405.   [8] *Ber.* 1912, **45**, 394.

or diethyl sulphate or with the salts of the half esters of sulphuric acid, such as potas͘ium ethyl sulphate.[1] The isomeric alkyl nitrites are formed also in this reaction: with dimethyl sulphate and potassium nitrite the yield is about 50 per cent. of the theoretical.

A further example of this type of preparation is Kolbe's method, the interaction of an alkali nitrite and an α-halogen substituted fatty acid; distillation of an aqueous solution containing sodium nitrite and sodium chloracetate is the most convenient method for preparing nitromethane. It is presumed that nitroacetic acid is the intermediate and that this loses carbon dioxide:

$$CH_2Cl \cdot CO_2Na \longrightarrow CH_2(NO_2) \cdot CO_2Na \longrightarrow CH_3NO_2 + NaHCO_3.$$
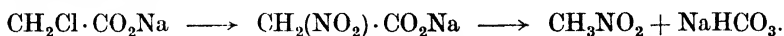
The yield is poor and under no conditions exceeds 50 per cent. of the theoretical value; the reaction is more complicated than the simple equation indicates. The α-bromo-derivatives of propionic, butyric, and heptoic acids behave in the same way, giving a 50 per cent. yield of the primary nitroparaffin,[2] but the reaction fails with acids in which the bromine is attached to a tertiary carbon atom; in this case the pseudo-nitrole is formed in small yield:

$$Me_2CBr \cdot CO_2H \longrightarrow Me_2C(NO_2)NO + CO_2.$$

A different method is that due to W. Wislicenus and A. Endres,[3] who showed that ethyl nitrate will condense in the presence of sodium ethoxide with compounds containing a reactive methylene group to give the sodium salt of the *aci*-form of a nitro compound (see p. 8). Thus benzyl cyanide gives the sodium salt of phenyl-isonitro-acetonitrile from which, by hydrolysis of the nitrile group and loss of carbon dioxide, phenylnitromethane can be obtained. This is the most convenient method of preparing this latter compound.

$$\phi CH_2 \cdot CN \longrightarrow \phi \cdot C(CN){:}NO \cdot ONa \longrightarrow \phi \cdot C(CO_2Na){:}NO \cdot ONa$$
$$\longrightarrow \phi CH_2 \cdot NO_2$$
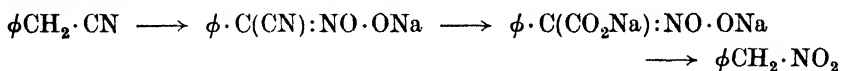
The nitroparaffins are colourless liquids, almost insoluble in water. They can be distilled unchanged under ordinary pressure (this is true even of $\phi \cdot (CH_2)_7 \cdot NO_2$), and their boiling-points are much higher than those of the isomeric nitrites (see table, p. 7), so that separation of nitrite and nitro compound is easy. This high boiling-point is characteristic of both aliphatic and aromatic nitro compounds and is in part connected with the large electric moment of the nitro group.[4] The value of μ for nitromethane is 3·19, and for amyl nitrite 2·27 D;[5] the work required to separate molecules from one another, one of the principal factors that

[1] P. Walden, *Ber.* 1907, **40**, 3214, 4301.

[2] V. Auger, *Bull. Soc. chim.* 1900, [iii], **23**, 333.

[3] *Ber.* 1902, 35, 1755; 1908, 41, 3334.

[4] N. V. Sidgwick, *J.C.S.* 1929, 1108; A. E. van Arkel, *Trans. Faraday Soc.* 1934, **30**, 698.

[5] E. C. E. Hunter and J. R. Partington, *J.C.S.* 1933, 309; A. Weissberger and R. Sängewald, *Ber.* 1932, **65**, 701.

determine the boiling-point of a compound, varies as the square of the electric moment of the molecules.

The dielectric constant of nitromethane is large (37), but most salts and acids which behave as strong electrolytes when dissolved in water or an alcohol, are weak electrolytes in nitromethane.[1] This behaviour is in disagreement with Nernst's simple rule which connects the ionizing power of a solvent with its dielectric constant. Its probable explanation is that for high ionization both the kation and anion must become solvated, and that nitromethane, though capable of forming co-ordinate links by contributing two electrons from an oxygen atom, contains no atom which can receive electrons to form such a link, and thus cannot unite by co-ordinate link formation with an anion: water or an alcohol can act both as donor and acceptor and thus can enter into solvation with both ions and decrease the probability of ionic association.

All nitroparaffins which contain hydrogen attached to the same carbon atom as the nitro group will dissolve in alkalis to form salts: the property is thus common to primary and secondary nitro compounds, but not to the tertiary. Victor Meyer, who discovered these facts, explained them by supposing that the highly negative nature of the nitro group rendered the hydrogen attached to the same carbon atom acidic, but that its influence did not extend to the next carbon atom. This explanation, however, soon proved insufficient. Victor Meyer had already found that the salts of these nitro compounds when warmed with an acid decomposed into a fatty acid and hydroxylamine,

$$R \cdot CH_2 \cdot NO_2 + H_2O \longrightarrow R \cdot CO_2H + NH_2OH,$$
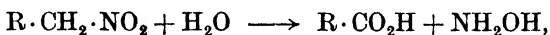
and J. U. Nef[2] showed that the salts of the nitro derivatives of methane, ethane, and propane are decomposed by excess of dilute mineral acid even at room temperature to nitrous oxide and an aldehyde (or ketone if the salt is derived from a secondary nitro compound). The original nitro compound can only be recovered if the solution is acidified with dilute acetic acid or with carbon dioxide. Nef further pointed to the fact that although the sodium salt behaved as though it were derived from a strong acid, the free nitro compound shows no acidic properties and only dissolves in caustic alkalis quite slowly. He suggested that the salt is derived from a tautomeric form of the nitro compound and proposed for it the structure $R \cdot CH{=}N{\diagup\diagdown}^O_{OH}$, which, written in the emended form $R \cdot CH{=}N{\diagup\diagdown}^O_{OH}$, is the structure of the isonitro form accepted to-day. Support for these views was rapidly forthcoming: A. F. Holleman[3] found that *m*-nitrophenylnitromethane gave a yellow sodium salt and that when the aqueous solution of this salt was treated with the equivalent of hydrochloric acid, it remained yellow at first and had a higher conductivity than that of

[1] L. Bruner, *Ber.* 1903, **36**, 3297; C. P. Wright, D. M. Murray-Rust and H. Hartley, *J.C.S.* 1931, 199; Murray-Rust, H. J. Hadow, and Hartley, ibid. 215.
[2] *Annalen*, 1894, **280**, 263.   [3] *Rec. trav. chim.* 1895, **14**, 121.

the sodium chloride it contained; on standing, however, the colour disappeared and the conductivity fell to that of the sodium chloride. This showed that the first effect of adding the mineral acid is to produce a yellow acidic compound which in time goes over into the colourless non-dissociated nitro compound. Hence the salt must be derived not from the nitro compound but from a more acidic tautomer.

A. Hantzsch and O. W. Schultze[1] almost immediately published results which showed that they had isolated this tautomeric form in two cases, those of phenylnitromethane and of the corresponding p-bromo compound. If carbon dioxide is passed into a solution of phenylnitromethane in aqueous sodium hydroxide, an oil separates slowly which is the true nitro compound, but if to the ice-cold solution a mineral acid is added, a white crystalline solid is precipitated, which when rapidly heated melts at 84°. They could show that both compounds had the same molecular weight and composition, and that on standing the solid form changed into the ordinary liquid nitro compound. With p-bromophenyl-nitromethane, the two isomers, similarly obtained, are both solid, the nitro form melting at 60° and the isonitro at 89–90°.

In both cases the difference between the two isomers is the same: the true nitro compound gives no colour with ferric chloride, is only slowly soluble in caustic alkalis, and forms no salt with dry ammonia in solution in dry benzene. The isomeric form gives immediately a brown-red colour with ferric chloride (compare the colour with the enolic form of aceto-acetic ester), is a strong acid immediately soluble in sodium hydroxide or sodium carbonate solution, and forms a salt with dry ammonia. In both cases the acidic form reverts to the other form on standing. The acidic form contains a hydroxyl group, since it reacts with phenyl isocyanate and yields methane when treated with methyl magnesium iodide. Two structures for the compound have been put forward.

$$\text{I. } R\cdot CH = N\underset{OH}{\overset{O}{\diagup}} \qquad \text{II. } R\cdot CH \underset{O}{\overset{\longrightarrow}{\diagdown}} N\cdot OH$$
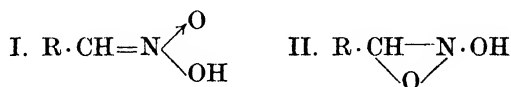
Of these the former, suggested by A. Michael,[2] is to be preferred. The second one was proposed because at one time certain oxime derivatives were thought to possess an analogous structure, but this has since been disproved; there is a marked parallel between keto-enol tautomerism ($-CH_2-CO- \rightleftharpoons -CH=C(OH)-$) and nitro-isonitro tautomerism which is best expressed in the first formula for the isonitro compound. Further we know that an isonitro compound readily reverts to the true nitro compound on standing, and this seems hardly compatible with a structure in which the carbon and oxygen atoms are united by a covalency.[3]

With bromine the isonitro compound reacts practically instantaneously

[1] *Ber.* 1896, **29**, 699, 2253; see also M. Konovalov, ibid. 2193.
[2] *J. pr. Chem.* 1888, **37**, 507.
[3] A. Hantzsch, *Ber.* 1912, **45**, 89.

at room temperature to give the bromonitro derivative: the true nitro compound does not give this reaction.

$$\text{>C:NO·OH} + Br_2 \longrightarrow \text{>CBr·NO}_2 + HBr$$
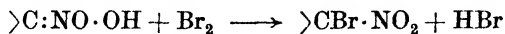
On this fact K. H. Meyer and P. Wertheimer[1] have based a method for estimating the amount of the isonitro form in a mixture of the two tautomers. To the mixture to be analysed a trace of ferric chloride is added and a bromine solution of known strength run in from a burette: the ferric chloride coloration disappears when an amount of bromine equivalent to the isonitro compound present has been added. They showed that for *aci*-phenylnitromethane in alcohol at 0° the rate of change was quite slow, after 4 hours 83 per cent. was still unchanged, and after 29 hours 30 per cent., and that eventually no *aci*-form could be detected: the equilibrium, if there is a true equilibrium, is very much in favour of the true nitro form. As in the case of keto-enol tautomerism, however, the introduction of substituents alters the position of equilibrium; thus *p*-nitrophenylnitromethane gives a true equilibrium, the position of which depends on the solvent; in pyridine there is 16 per cent. of the *aci*-form at equilibrium.

The influence of the solvent on the position of equilibrium varies with the nature of the group attached to the carbon atom carrying the nitro group. With *p*-nitrophenylnitromethane in hydroxylic solvents, and especially in aqueous methyl alcohol, the equilibrium percentage of *aci*-form is higher than in hydrocarbon solvents. Nitroacetophenone, $\phi \cdot CO \cdot CH_2 \cdot NO_2$, shows the opposite behaviour; in toluene the *aci* content at equilibrium is 10·3 per cent. and in aqueous methyl alcohol only 2·7 per cent. This influence of the solvent on equilibrium is known to be connected with the relative solubilities of the two tautomers in the solvent; if one form (A) is more soluble than the other (B) in one solvent, but less soluble in a second solvent, then on going from the first solvent to the second, the equilibrium will shift in favour of (B) (the van't Hoff-Dimroth relation).[2] Hence these results show that with *p*-nitrophenylnitromethane the *aci*-form, when compared with its tautomer, is more soluble in water than in toluene, while the reverse is true in the case of nitroacetophenone.

This conclusion is not surprising in the case of the *p*-nitro compound, since a hydroxylic substance such as the *aci*-form would be expected to show a greater solubility in a hydroxylic solvent than the isomeric true nitro form, and also an abnormally small solubility in hydrocarbons. With the nitroketone, the relative solubilities are exactly the reverse; the *aci*-form does not behave as a hydroxylic solute, but is more normal as a solute than the true nitro compound. This behaviour recalls that of the keto and enol forms of β-ketonic esters, such as acetoacetic ester, and of β-diketones; here again the enol, though at first glance a hydroxylic compound, is less soluble in water than the keto form and more soluble in hexane. The reason for this behaviour lies in the fact that the hydrogen

[1] *Ber.* 1914, **47**, 2374.   [2] *Annalen*, 1910, **377**, 127.

atom of the hydroxyl group is united to the oxygen atom of the car-
bonyl group by a hydrogen-bond, their relative positions in space
being such that a six-membered ring can form with ease (III).[1] A similar

III. $\begin{array}{c} -C-CH=C- \\ \| \quad\quad | \\ O\cdots H----O \end{array}$
　　IV. $\begin{array}{c} -C-CH=N\rightarrow O \\ \| \quad\quad | \\ O\cdots H----O \end{array}$　　$\begin{array}{c} -C=CH-N\rightarrow O \\ | \quad\quad\quad \| \\ O-H \cdots O \end{array}$

V. $O_2N\langle\bigcirc\rangle-CH=N\rightarrow O$
　　　　　　　　　$\underset{HO}{|}$
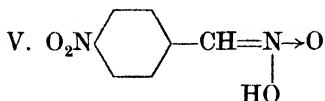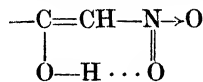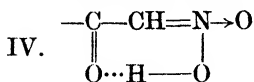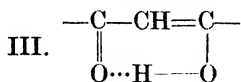
explanation must be true for the nitro-ketone; it differs from p-nitro-
phenylnitromethane (V) because in the latter compound there is no
possibility of the formation of a chelate ring. But there are important con-
sequences. When Kurt H. Meyer investigated the nitro-ketone, he found it
difficult to decide whether the acidic tautomer was the *aci*-form of the
nitro group or the enolic form of the ketone group, both possibilities of
tautomerism being present in the molecule. Its structure might be repre-
sented by either of the two formulae shown in (IV); the first is an *aci*-nitro
compound with a hydrogen-bond to the ketonic oxygen atom, and the
second an enol with a hydrogen-bond to an oxygen atom of the nitro
group. These two formulae are, however, identical, since, as is explained
in the Introduction, the essence of hydrogen-bond formation is resonance
between two such structures. Hence the absence of hydroxylic properties
in the acidic tautomer implies that there is no distinction whatever be-
tween the enolic and *aci*- forms and Kurt Meyer's difficulty has no real
existence. This view finds strong support in the products which are
obtained when the nitro-ketone is treated with diazomethane.[2] An enol
is converted by diazomethane into its methyl ether, —C(OMe):CH—,
while an *aci*-nitro compound gives its methyl ester, —CH=NO·OMe; the
nitro-ketone under discussion gives a mixture of the enolic ether and the
nitronic ester, the latter comprising about two-thirds of the total product.
Hence the acidic tautomer of ω-nitroacetophenone is best regarded as a
resonance-hybrid, a conclusion upheld both by its physical and chemical
properties.

The rate at which the *aci*-form of a nitro compound changes into
the true nitro form is affected to an enormous extent by traces of
acids or bases which act as catalysts. This was most clearly shown
by T. M. Lowry and E. H. Magson[3] in the case of nitrocamphor, where
the two tautomers have different optical rotations and thus the rate of
change can be conveniently followed in the polarimeter. Some of the
more surprising of their results are as follows: in carefully purified benzene
the time required for 99·5 per cent. of the total change to proceed is 12
days; it is reduced to half this value if the secondary base piperidine is
added in a concentration of $N/10^7$, which is equivalent to adding one-tenth

[1] N. V. Sidgwick, *J.C.S.* 1925, **127**, 907.
[2] F. Arndt and J. D. Rose, *J.C.S.* 1935, 1.　　　[3] *J.C.S.* 1908, **93**, 107, 119.

of a gram to one ton of benzene. If the piperidine concentration is raised to $N/10^4$, the period is 10 minutes. The traces of alkali from glass have an enormous effect; one solution gave a period of 66 days in glass and 6 years in silica. The result of this effect is that the addition of a trace of an acidic substance to a solution in a glass vessel reduces the rate of change because it neutralizes the alkali from the glass, while further addition accelerates the change, because the acid is itself a catalyst. Thus Lowry and Magson found that in chloroform with $N/1,000$ trichloracetic acid the rate of change was infinitely slow, while the period for $N/100$ acid was $5\frac{1}{2}$ hours and for $N/10$ acid 33 minutes. Rates of tautomeric change are in general susceptible to catalysis, but these results with nitrocamphor are very striking; they support the view that the two constituent reactions of the tautomeric equilibrium do not proceed except in the presence of a catalyst.[1]

The rate of change of the *aci* into the true nitro form can also be measured by conductivity methods, taking advantage of the fact that the *aci*-form is an electrolyte and the true nitro compound is not,[2] and by means of K. H. Meyer's bromine titration method.[3] The results of such measurements show that the undissociated molecule of the *aci*-form does not change into the true nitro form; the rate is proportional to the concentration of the ion of the *aci*-form, and the true nitro compound is only formed by a slow reaction between this ion and the hydrogen ion. The undissociated *aci*-compound is a somewhat unstable compound especially in acid solution. It is for this reason that addition of a mineral acid to a solution of the sodium salt of a nitro compound usually results in the decomposition of the compound, unless it is sufficiently insoluble under the conditions used to crystallize out. With the simpler *aci*-nitro compounds there is a certain amount of decomposition to nitrous oxide and an aldehyde (or ketone), but the compound mainly rearranges to a hydroxamic acid, or with hydrogen chloride in ethereal solution to a hydroxamic chloride. This rearrangement is accompanied by the appearance of the blue colour typical of a nitroso compound,[4] and in one case by the action of hydrogen chloride on isonitroethane in ether W. Steinkopf and B. Jurgens[5] isolated the intermediate chloro-nitrosoethane, $CH_3 \cdot CHCl \cdot NO$. Hence it appears that the course of the reaction is a primary rearrangement to a nitroso alcohol, which may react with hydrogen chloride to give a chloronitroso compound, followed by migration of the hydrogen atom to give a hydroxamic acid or its derivative:

$$R \cdot CH{:}NOOH \longrightarrow R \cdot CHOH \cdot NO \longrightarrow R \cdot C(OH){:}NOH$$
$$\downarrow$$
$$R \cdot CHCl \cdot NO \longrightarrow R \cdot CCl{:}NOH.$$
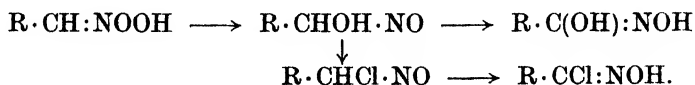
[1] K. J. Pedersen, *Kgl. Danske Videns. Selskab. Math.-fys.* 1932, No. 12, 1.

[2] A. Hantzsch, *Ber.* 1896, **29**, 2251; 1899, **32**, 607; G. E. K. Branch and J. Jaxon-Deelman, *J. Amer. C. S.* 1927, **49**, 1765.

[3] R. Junell, *Svensk Kemisk Tidskrift*, 1934, **46**, 125.

[4] E. Bamberger and E. Rust, *Ber.* 1902, **35**, 45.   [5] *J. pr. Chem.* 1911, **84**, 686.

The formation of hydroxylamine and a carboxylic acid on heating with aqueous mineral acids, which Victor Meyer observed, is, of course, the hydrolysis of the hydroxamic acid.

This rearrangement to a hydroxamic acid also takes place slowly if the true nitro compound is kept warm in the presence of a mineral acid. The rate at which it occurs can be measured by titrating the hydroxamic acid with potassium bromate, and proves to be identical with the rate at which the nitro compound reacts with bromine at the same temperature and with the same mineral acid concentration. The bromination rate is independent of the bromine concentration, as is the rate of the reaction between halogens and acetone, and is unimolecular with respect to the nitro compound. It thus appears that the rate measured is the rate of change of the nitro compound into the *aci*-form which in the presence of bromine reacts, as has been indicated, very rapidly with the bromine, or in its absence rearranges to the hydroxamic acid at a rate faster than that of the tautomeric change.[1]

The salts of the aliphatic isonitro compounds present many features of interest which cannot be discussed here. Those derived from nitromethane are exceptional in that they pass easily into fulminates. Thus though nitroethane gives a colourless salt with mercuric chloride of composition $CH_3 \cdot CH:NO_2 \cdot HgCl$, which is not explosive, nitromethane gives mercuric fulminate, $Hg(ONC)_2$, by loss of water from the *aci*-nitro salt.[2]

$$CH_2:NO \cdot Ohg \longrightarrow CNOhg + H_2O \qquad (hg = \tfrac{1}{2}Hg)$$
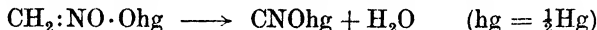
Similarly the sodium salt of nitromethane can be obtained by interaction of nitromethane with sodium ethoxide in alcoholic solution, and crystallizes with one molecule of alcohol, in which form it is fairly stable. It explodes on heating, however, and even wetting it with water generates enough heat to convert it into the fulminate; it turns yellow and explodes.

The salts of many aliphatic nitro derivatives, particularly those of the polynitro compounds and of the α-nitro-ketones were found by A. Hantzsch[3] to exist in more than one form which differed markedly in their colour, although they show the same molecular weights and the same conductivity in solution. Thus Hantzsch states that the salts of *p*-nitrophenylnitromethane can be obtained in colourless, yellow, red, green, and violet forms. No satisfactory explanation of these observations has yet been offered.

Of the esters of the *aci*-nitro compounds only the methyl esters have been prepared ($R \cdot CH:NO \cdot OMe$). They are curiously unstable substances obtained by the action of diazomethane on the nitro compound in either of its two tautomeric forms.[4] With the *aci*-form the reaction is very vigorous, while with the true nitro compound it is slow; it may be that slow tautomeric change of the nitro compound into the *aci*-form must

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[1] R. Junell, *Z. phys. Chem.* 1929, A, **141**, 89; *Arkiv f. Kemi*, 1934, **11** B, No. 30.
[2] J. U. Nef, *Annalen*, 1894, **280**, 273.
[3] *e.g. Ber.* 1907, **40**, 1523.   [4] F. Arndt and J. D. Rose, *J.C.S.* 1935, 1.

precede reaction, but it is possible that the true nitro form is itself capable of reacting slowly. The nitronic ester from *p*-bromophenylnitromethane is a colourless solid melting at 65°; that from phenylnitromethane is an oil. All the esters show a characteristic and violent decomposition when they are heated to 70–90°, in which the methyl group is eliminated as formaldehyde, and the nitro compound is reduced to an aldoxime:

$$\phi \cdot \text{CH:NO} \cdot \text{OCH}_3 \longrightarrow \phi \cdot \text{CH:NOH} + \text{CH}_2\text{O}.$$
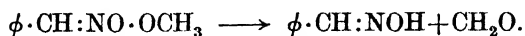
Unlike most esters they cannot be hydrolysed to alcohol and acid since with both alkalis and mineral acids profound decompositions take place. On boiling with hydrochloric acid, a certain amount of an oxadiazole is formed.

$$\phi \cdot \text{CH:NO} \cdot \text{OMe} \longrightarrow \phi \cdot \text{C} \underset{\text{N}=\text{C} \cdot \phi}{\overset{\text{N}-\text{O}}{\diagdown}}$$
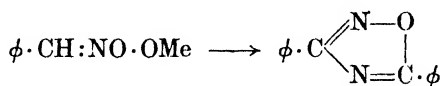
There is one series of observations on the salts of aliphatic nitro compounds which deserves detailed discussion because of its bearing on their structure. R. Kuhn and H. Albrecht[1] prepared 2-nitrobutane in both laevo- and dextro-rotatory forms from optically active *sec*-butyl alcohols:

$$\underset{\text{Me}}{\overset{\text{Et}}{\diagdown}} \text{CH} \cdot \text{OH} \longrightarrow \underset{\text{Me}}{\overset{\text{Et}}{\diagdown}} \text{CH} \cdot \text{I} \longrightarrow \underset{\text{Me}}{\overset{\text{Et}}{\diagdown}} \text{CH} \cdot \text{NO}_2.$$
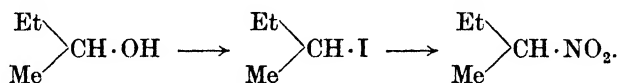
The optical activity is, of course, due to the asymmetric carbon atom present in the molecule. They then studied the effect of salt formation on the activity. They found that if to the methyl alcoholic solution of the active nitro compound aqueous caustic soda were added in excess, the activity completely disappeared. If the alkali was not in excess, there was an activity due to incomplete salt formation, as was shown by the fact that after dilution with water and extraction with ether the solution was no longer active, the uncombined active nitro compound having been removed in the ether. If, however, they added a methyl alcoholic solution of sodium or potassium methoxide to a solution of the nitro compound in methyl alcohol, the activity remained and could be shown to be due to a salt of the nitro compound; it could not be due to incomplete salt formation because there was no diminution in activity, either on adding excess of sodium methoxide or on diluting with water and extracting with ether. Addition of a large amount of ether to the active alcoholic solution gave a white solid, which on dissolving in cold methyl alcohol gave an active solution. Analysis showed that the solid was not the pure salt; its sodium content was too high and it appeared to be contaminated with sodium methoxide. The active solution reacts rapidly with bromine and gives a bromonitro compound, $\text{MeEtCBr} \cdot \text{NO}_2$, which is itself optically active.

These results have been confirmed by R. L. Shriner and J. H. Young,[2]

[1] *Ber.* 1927, **60**, 1297.   [2] *J. Amer. C. S.* 1930, **52**, 3332.

working with a different optically active nitro compound, 2-nitro-octane, $C_6H_{13} \cdot CHNO_2 \cdot CH_3$. They record no observations with aqueous caustic soda, but used sodium ethoxide in ethyl alcohol. They further showed that if sodium ethoxide is added to the nitro compound in alcohol and the resulting active solution is acidified with alcoholic hydrogen chloride at $-70°$, the nitro compound which is recovered is still optically active and shows a rotation which is 71·2 per cent. of that of the starting material.

The views which have been expressed above on the structure of the salts of nitro compounds can clearly give no adequate explanation for these facts. If the nitro compound (VII) forms a salt whose anion is correctly allotted the structure (VIII), the salt cannot be optically active because the formation of a true double bond between carbon and nitrogen means that the ion (VIII) possesses a plane of symmetry and the activity must disappear. If the ion has a ring structure (IX) it could be optically

VII. $\overset{R}{\underset{R'}{>}}C\overset{H}{\underset{NO_2}{<}}$ VIII. $\overset{R}{\underset{R'}{>}}C=N\overset{O^-}{\underset{O}{<}}$ IX. $\overset{R}{\underset{R'}{>}}C-N-O^-$ (with O below)

X. $\overset{R}{\underset{R'}{>}}C\leftarrow N\overset{O^-}{\underset{O}{<}}$
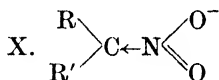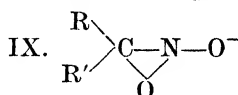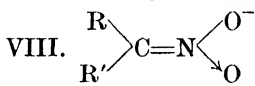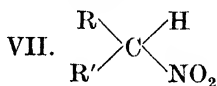
active, but such a formula is held almost universally to be quite unsatisfactory, because it fails to account for the similarity between nitro-isonitro tautomerism and keto-enol tautomerism. Both Kuhn and Shriner rightly reject the three-ring formula; they are of opinion that the best solution is to accept for the ion of the *aci*-form a structure which may be written as in X, in which the link between carbon and nitrogen is a co-ordinate link formed by two electrons from the nitrogen atom. This formula might also be written with a semi-polar double bond (XI) or, with dots indicating electrons, as in XII. All these formulae are different ways of expressing the same thing. It will be seen that on this view the

XI. $\overset{R_1}{\underset{R_2}{>}}\overset{-}{C}-\overset{+}{N}\overset{O^-}{\underset{O}{<}}$ XII $R_2 : \overset{R_1}{\underset{}{C}} : N :: O :$ (with O below)

XIII. $\overset{R_1}{\underset{R_2}{>}}S-R_3 \; [Br]$ XIV. $\overset{R_1}{\underset{R_2}{>}}S\rightarrow O$
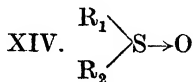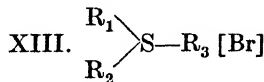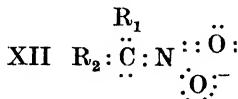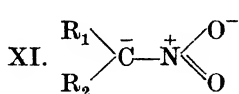
carbon atom is essentially tricovalent; it is somewhat analogous to the sulphur atom in a sulphonium cation or a sulphoxide (XIII and XIV), and since both the latter compounds are known to be capable of enantiomorphism (the three attached groups not lying in the same plane with the sulphur atom), the activity of the nitro ion is accounted for.

This solution of the problem possibly finds a certain amount of support in the fact that one compound seems to be known in which carbon does occur in this curious state of combination, three attached groups and a 'lone-pair' of electrons. This is the case of a somewhat unstable compound

prepared by C. K. Ingold and J. A. Jessop[1] by the action of alkali on fluorenyl-9-dimethylsulphonium bromide.

$$\begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!\!>\!\!CHBr + SMe_2 \longrightarrow \begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!\!>\!\!CH\cdot SMe_2\,[Br] \xrightarrow{NaOH} \begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!\!>\!\!C\leftarrow SMe_2$$
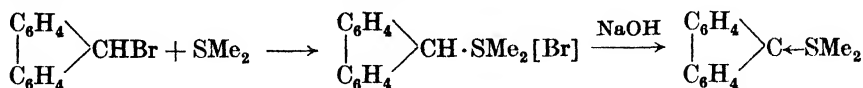
The support is not, however, strong. Ingold's compound decomposes in a few hours in air at room temperature and very rapidly in solution, while the isonitro ion is quite stable. Further, the alternative formula, $>\!C\!=\!SMe_2$, for the sulphur compound is very improbable, because it involves for the sulphur atom a group of ten valency electrons which is not found in any other sulphur compound,[2] while for the isonitro ion there is the alternative structure (VIII), and there seems no adequate reason why the co-ordinate structure (X) should be assumed in preference to this alternative. In the case of the N-methyl ether of an oxime (XV), which differs from the isonitro ion only in the substitution of a methyl group for the oxygen atom, the evidence is complete that the structure is (XV) and is analogous to (VIII) and not to (X). Such compounds occur in two geometrically isomeric forms which is conclusive proof of a true double bond between carbon and nitrogen (see p. 178). Why two compounds of such similar nature should assume structures so profoundly different as (X) and (XV) is a question to which it is hard to find a satisfactory answer, and this fact must be held to be strong evidence against the probability of formula (X).

$$\text{XV.} \quad \begin{matrix} R \\ \\ R' \end{matrix}\!\!\!>\!\!C\!=\!N\!<\!\!\!\begin{matrix} O \\ \\ CH_3 \end{matrix} \qquad \text{XVI.} \quad \begin{matrix} R \\ \\ R' \end{matrix}\!\!\!>\!\!CH\cdot N\!<\!\!\!\begin{matrix} ONa \\ \!\!-OCH_3 \\ O \end{matrix}$$
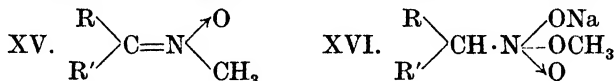
But the observed facts of the optical activity remain. No satisfactory explanation of them has been established. It is, however, possible that the optically active salt, which undoubtedly exists, is not the salt

$$EtMeC\!:\!NO\cdot ONa$$
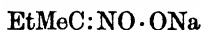
at all. Kuhn and Albrecht were unable to obtain it in an analytically pure condition. When it is remembered that the sodium salt of nitromethane retains a molecule of alcohol tenaciously in the solid state, the possibility presents itself that the nitro compound can, in the presence of alcohol, form a salt by direct union with a molecule of sodium alkoxide and not by substitution of its acidic hydrogen atom by sodium. If this is the case, the addition would involve the nitro group alone and the centre of asymmetry of the molecule, the carbon atom, would be unaffected, so that such a salt could retain the optical activity. It is premature to suggest a structure for this addition-salt, but a formula such as (XVI) is not impossible. The formation of the substitution-salt could take place by loss of a molecule of alcohol from the addition-salt, and this might well be a slow reaction at low temperatures. Racemization was certainly observed in some conditions by both sets of workers, and it is possible that this is the manifestation of the change of the addition-salt into the substitution-salt. The rapid

[1] *J.C.S.* 1930, 713.   [2] See *Ann. Report C. S.* 1933, 30, 125.

formation of a bromonitro compound, $RR'CBr\cdot NO_2$, on addition of bromine seems to have been regarded by both Kuhn and Shriner as proof that the nitro compound was in the *aci*-form. The proof is not, however, conclusive; we know that in acid solution *aci*-nitro compounds react rapidly with bromine whereas true nitro compounds do not, but it does not necessarily follow that the same difference persists in the presence of alkali. The problem is still unsolved, but provisionally it seems better to accept some solution in terms of salt formation by addition rather than in terms of a structure such as (X).

This conclusion is upheld by the results which Arndt and Rose obtained in their investigation of the action of diazomethane on the aliphatic nitro compounds.[1] If formula (X) is correct and salt formation is simply removal of a proton from the carbon atom, the action of diazomethane might be expected to lead to a compound in which the entering methyl group became attached to that carbon atom, as in the case of a sulphone of the structure $R\cdot CH_2\cdot SO_2\cdot R'$. The product is, however, always an O-methyl compound, the nitronic ester, whose properties accord well with a structure related to the *aci*-form (VIII). Hence from this point of view also the formulation of the *aci*-anion as (X) seems very unlikely.

To return to the chemical reactions of the aliphatic nitro compounds: the methylene group of a primary compound $R\cdot CH_2\cdot NO_2$ is a reactive methylene group in the same sense as in a compound containing the group $—CH_2\cdot CO—$. It is thus able to condense with aldehydes, with the production either of an alcohol (A) which easily passes into an unsaturated compound (B), or else of a 1,3-dinitro compound, arising from two molecules of the nitro compound and one of the aldehyde (C).

$$R\cdot CHO + H_2C\overset{R'}{\underset{NO_2}{<}} \longrightarrow R\cdot CHOH\cdot CH\overset{R'}{\underset{NO_2}{<}} \longrightarrow RCH:C\overset{R'}{\underset{NO_2}{<}}$$
$$\text{(A)} \qquad\qquad\qquad \text{(B)}$$

$$R\cdot CHO + \begin{matrix} H_2C\overset{R'}{\underset{NO_2}{<}} \\ H_2C\overset{R'}{\underset{NO_2}{<}} \end{matrix} \longrightarrow \begin{matrix} R'\cdot CH\cdot NO_2 \\ | \\ R\cdot CH \\ | \\ R'\cdot CH\cdot NO_2 \end{matrix}$$
$$\text{(C)}$$
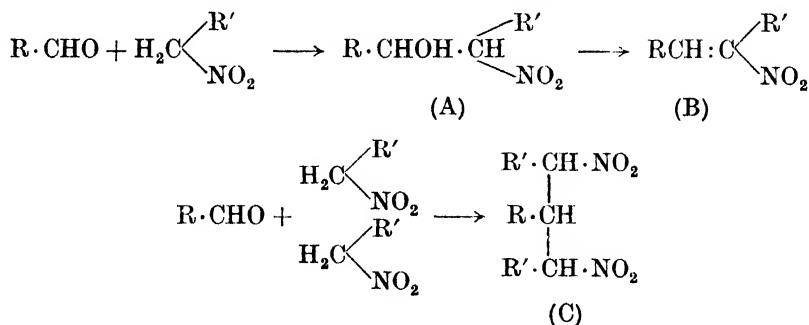
The unsaturated product (B) is the most usually obtained and sometimes it appears as a mixture of the two possible geometrically isomeric forms.[2] The condensing agents which have been used to bring about these reactions are zinc chloride at 160°, primary aliphatic amines such as ethylamine, and alcoholic potash at 0°, when the salt of the nitro alcohol (A) is often formed and passes into the olefine (B) on acidifying; secondary bases, such as piperidine do not act as condensing agents.[3] Another con-

[1] *J.C.S.* 1935, 1. [2] F. Heim, *Ber.* 1911, **44**, 2016.
[3] E. Knoevenagel and L. Walter, *Ber.* 1905, **37**, 4502.

densation reaction of the sodium salt of an *aci*-nitro compound is with $\alpha\beta$-unsaturated ketones; it also takes place, though less readily, with unsaturated esters. It is similar to the Michael condensation of compounds such as the sodium derivative of malonic esters with the same types of compounds. The product is the sodium salt of a γ-nitro-ketone or ester,[1] which with acids gives the nitro compound.

$$R \cdot CH : CH \cdot CO \cdot R' + R'' \cdot CH : NO \cdot ONa \longrightarrow R \cdot \underset{\underset{R'' \cdot \dot{C} : NO \cdot ONa}{|}}{CH} \cdot CH_2 \cdot CO \cdot R'$$

$$\longrightarrow R \underset{\underset{R'' \cdot \dot{C}H \cdot NO_2}{|}}{CH} \cdot CH_2 \cdot CO \cdot R'$$
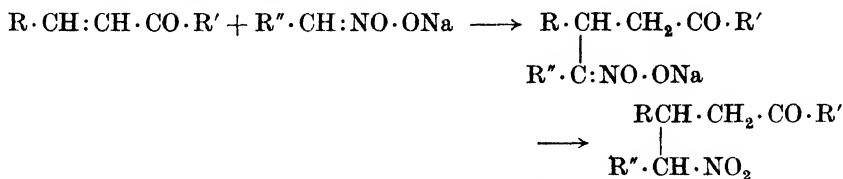
By means of this reaction Kohler and Engelbrecht[2] prepared a compound, bromination of which, followed by elimination of hydrogen bromide with potassium acetate, gave a nitrocyclopropane derivative.

$$\underset{\underset{\dot{C}H_2 \cdot NO_2}{|}}{\phi \cdot CH} \cdot CH_2 \cdot CO \cdot \phi \longrightarrow \underset{\underset{\dot{C}H_2 \cdot NO_2}{|}}{\phi \cdot CH} \cdot CHBr \cdot CO \cdot \phi \longrightarrow \underset{\underset{\dot{C}H \cdot NO_2}{\diagdown\diagup}}{\phi \cdot CH} \cdot CH \cdot CO\phi$$
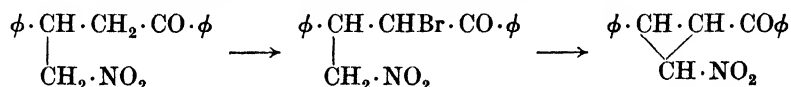
The type of reaction exhibited by a nitroparaffin with nitrous acid depends on the number of hydrogen atoms attached to the carbon atom carrying the nitro group. Primary nitro compounds give nitrolic acids which form characteristic red salts, secondary nitro compounds give pseudo-nitroles which are blue in solution, and the tertiary compounds do not react with nitrous acid. This difference in behaviour was used by Victor Meyer as the basis of a method to distinguish between primary, secondary, and tertiary alcohols: the alcohol is converted into the iodide which is then distilled with silver nitrite, giving a mixture of nitro compound and nitrite; the latter need not be removed. This product is dissolved in aqueous caustic potash, sodium nitrite added, and then sulphuric acid slowly. A red colour which disappears when the solution becomes acid indicates a primary compound; a blue colour, or a substance soluble in chloroform with a blue colour, a secondary compound. The nitrolic acids have the general formula $R \cdot C \!\! \diagup^{NOH}_{\diagdown NO_2}$ and are formed from primary nitro compounds and nitrous acid by loss of water; the reaction resembles the formation of an isonitroso compound from certain ketones.

$$-CO \cdot CH_2 - + ONOH \longrightarrow -CO \cdot C(:NOH) - + H_2O$$
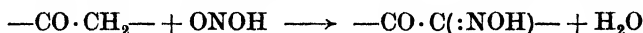
This structure is confirmed by the fact that Victor Meyer obtained them from dibromo-nitro compounds and hydroxylamine:

$$R \cdot CBr_2 \cdot NO_2 + H_2NOH \longrightarrow RC \!\! \diagup^{NOH}_{\diagdown NO_2} + 2HBr.$$

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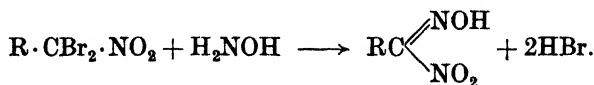
[1] E. P. Kohler, *J. Amer. C. S.* 1916, **38**, 889; E. P. Kohler and H. F. Engelbrecht, ibid. 1919, **41**, 764. [2] Ibid. 1919, **41**, 1379.

Their salts as ordinarily obtained are bright red and very explosive when solid: from them the nitrolic acid can be regenerated by mineral acids. On wa ming or exposure to light they are transformed into colourless salts, which Hantzsch called isonitrolates,[1] and from which the nitrolic acid cannot be obtained. With acids these are decomposed to nitrous acid and the polymer of a nitrile oxide ($R \cdot CNO$) (see p. 345).

The pseudo-nitroles from the secondary nitro compounds show the usual behaviour of true nitroso compounds (see p. 204). In solution they are blue, but the solid form is usually colourless, although $\alpha\gamma$-diphenylpropane-β-ψ-nitrole ($\phi \cdot CH_2)_2C(NO)NO_2$ is blue in the solid state even at liquid-air temperatures and seems incapable of existing in the normal bimolecular colourless form.[2] Their structure is shown by this fact to be

$$R_2C\diagdown^{NO}_{NO_2}$$ and this has been confirmed by O. Piloty and A. Stock[3] who

showed that bromonitrosopropane, obtained by the action of bromine on acetoxime (see p. 207), reacts with silver nitrite to give isopropyl-ψ-nitrole.

$$(CH_3)_2C\diagdown^{Br}_{NO} \longrightarrow (CH_3)_2C\diagdown^{NO_2}_{NO}.$$
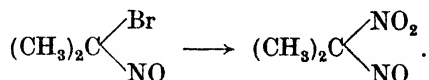
Chloropicrin, as trichlornitromethane, $CCl_3(NO_2)$, is usually called, is formed when almost any organic compound is treated destructively with *aqua regia*. It is usually prepared by the action of sodium hypochlorite or of chlorine on picric acid or one of its salts. It is a liquid boiling at 112°, and at that temperature slowly decomposes into carbonyl chloride and nitrosyl chloride:

$$CCl_3(NO_2) \longrightarrow COCl_2 + NOCl.$$
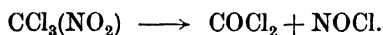
It is an extremely active lung irritant, which is fatal to man when breathed at a concentration of 1 part in 20,000 of air. It was used in gas-shell during the Great War, being introduced in 1916, and finds an extensive use as an insecticide, fumigant, and disinfectant.[4]

Unsaturated Nitro Compounds. The introduction of the nitro group by direct nitration takes place much more easily with unsaturated compounds than with the paraffins. Thus $\alpha\alpha$-diphenylethylene can be nitrated with mixed nitric and sulphuric acid to the β-nitro compound, $\phi_2C:CH \cdot NO_2$.[5] In some of these cases it is clear that the mechanism of the reaction is the addition of nitric acid to the double bond followed by loss of water, a fact which is of interest in connexion with aromatic nitration. Thus H. Wieland and E. Sakellarios[6] found that when ethylene is treated with nitric acid the product is a mixture of β-nitroethyl nitrate,

$$CH_2NO_2 \cdot CH_2ONO_2,$$
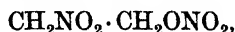
[1] *Ber.* 1909, **42**, 892.   [2] H. Rheinboldt and M. Dewald, ibid. 1927, **60**, 249.
[3] Ibid. 1902, **35**, 3093.
[4] An interesting account of this compound is given by K. E. Jackson, *Chem. Rev.* 1934, **14**, 251.   [5] E. P. Kohler and N. L. Drake, *J. Amer. C. S.* 1923, **45**, 1287.
[6] *Ber.* 1919, **52**, 898; 1920, **53**, 201.

and glycol dinitrate, $CH_2ONO_2 \cdot CH_2ONO_2$; the former is the ester produced by esterification of β-nitroethyl alcohol which arises by addition of nitric acid to the ethylene. This ester and the alcohol from which it is derived (prepared by the action of silver nitrite on ethylene iodohydrin, $CH_2I \cdot CH_2OH$) are converted into nitroethylene by the action of phosphorus pentoxide or sodium bisulphate, with loss of nitric acid and of water respectively. Nitroethylene is a practically colourless liquid boiling at $98 \cdot 5°$. It has an extremely irritating effect on the mucous membrane and Wieland has compared it with acrolein, $CH_2 : CH \cdot CHO$, which it further resembles in its great tendency to polymerization. This process is catalysed by light, by water, and, above all, by alkalis, and leads to a variety of products, among which the principal is an amorphous polymer of high molecular weight, which is almost certainly a long-chain compound. The addition of nitric acid to a double bond with formation of a nitro-alcohol is a not infrequent phenomenon; it has been observed with $\alpha\alpha$-diphenylethylene, and phenanthrene,[1] and with tetrahydro-carbazole.[2] Unsaturated nitro compounds are also often obtained as the product of the addition of nitrogen peroxide to ethylenic compounds, a reaction which is discussed below.

Saturated nitro compounds can rarely be obtained by the catalytic reduction of the unsaturated compounds: as a rule the nitro group is itself reduced, and in this respect they differ from unsaturated ketones.[3] The product is usually either an oxime, $RCH_2 \cdot CR' : NOH$, or else a bimolecular compound, e.g.

$$R \cdot CH \cdot CH_2 \cdot NO_2$$
$$|$$
$$R \cdot CH \cdot CH_2 \cdot NO_2.$$
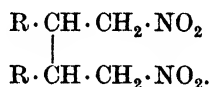
Polynitro Compounds

The dinitro compounds in which the two nitro groups are attached to the same carbon atom can be obtained:

(1) by the oxidation of the pseudonitroles with chromic acid.

(2) by the action of potassium nitrite and alcoholic potash on the bromo-nitro compound formed by bromination of a nitro compound.

$$CH_3 \cdot CH_2 \cdot NO_2 \longrightarrow CH_3 \cdot CHBr \cdot NO_2 \longrightarrow CH_3 \cdot CH(NO_2)_2$$

(3) by the action of concentrated nitric acid on certain ketones; thus 1,1-dinitroethane, $CH_3 \cdot CH(NO_2)_2$, can be obtained from diethylketone, methylethylketone or ethylpropylketone.[4]

The primary dinitro compounds of this type, e.g. those containing the group $—CH(NO_2)_2$, are strong monobasic acids, and in solution almost

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[1] H. Wieland and F. Rahn, *Ber.* 1921, **54**, 1770.

[2] W. H. Perkin and S. G. P. Plant, *J.C.S.* 1923, **123**, 676.

[3] A. Sonn and A. Schellenberg, *Ber.* 1917, **50**, 1513; E. P. Kohler and N. L. Drake, *J. Amer. C. S.* 1923, **45**, 1281.

[4] M. G. Chancel, *Bull. Soc. chim.* 1879, [ii], **31**, 504; M. Fileti and G. Ponzio, *J. pr. Chem.* 1897, [ii], **55**, 195.

certainly exist as isonitro compounds, $-C\underset{NO\cdot OH}{\overset{NO_2}{\diagdown}}$. The salts of these compounds are yellow, unlike those of the mononitro compounds. On reduction one nitrogen atom is readily lost, and the product is an oxime which can be further reduced to an amine:[1]

$$R\cdot CH(NO_2)_2 \longrightarrow R\cdot CH:NOH \longrightarrow R\cdot CHNH_2.$$

When heated with potassium hydroxide, they give ammonia, potassium nitrite, and a fatty acid. Ponzio[2] has argued that the ease with which one nitrogen is removed indicates that both nitrogen atoms cannot be attached to carbon and that the true formula is $R\cdot CH\underset{O\cdot NO}{\overset{NO_2}{\diagdown}}$. We have seen already, however, that in the *aci*-form of even a mononitroparaffin the nitrogen-carbon link is easily split, and hence this argument carries little weight. The method of preparation of the substances indicates that they are true dinitro compounds. The same loss of a nitro group takes place with other polynitro compounds, such as tetranitromethane, where there is indisputable evidence that the nitrogen atoms are attached to carbon (p. 247).

The 1,2-dinitro compounds such as the derivatives of 1,2-dinitroethane, $R\cdot CHNO_2\cdot CHNO_2\cdot R$, can often be obtained by addition of nitrogen peroxide to the corresponding ethylenic compounds, $R\cdot CH:CH\cdot R$, usually in solution in an inert solvent such as benzene. The constitution of these addition compounds was a matter of dispute for many years, until H. Wieland and F. Reindel[3] showed that the compound obtained from stilbene ($\phi\cdot CH:CH\cdot\phi$) and nitrogen peroxide is identical with that formed by the interaction in ether of bromophenylnitromethane and finely divided silver and hence must be 1,2-dinitro-1,2-diphenylethane, $\phi\cdot CHNO_2\cdot CHNO_2\cdot\phi$. Compounds of this constitution behave somewhat like the corresponding dichloro or dibromo compounds, in that, especially in the presence of alkali, they can be converted into unsaturated compounds, in this case by loss of nitrous acid:

$$R\cdot CHNO_2\cdot CHNO_2\cdot R \longrightarrow R\cdot CH:CNO_2\cdot R + HNO_2.$$
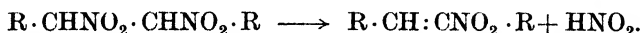
In some cases this reaction takes place with the greatest ease when water or alcohol is added: for example, cinnamic acid in dry benzene will absorb nitrogen peroxide to give a dinitro compound which crystallizes from the solution. If these crystals are washed with water, nitrous fumes and carbon dioxide are immediately evolved, and ω-nitrostyrene (phenylnitroethylene) is produced.[4]

$$\phi\cdot CH:CH\cdot CO_2H \longrightarrow \phi\cdot CHNO_2\cdot CHNO_2\cdot CO_2H$$
$$\longrightarrow \phi\cdot CH:CHNO_2 + CO_2 + HNO_2$$
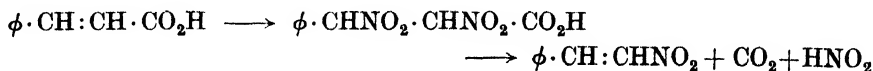
[1] G. Ponzio, ibid. 1902, [ii], **65**, 197.
[2] Ibid. 1903, [ii], **67**, 137.
[3] *Annalen*, 1921, **424**, 71.   [4] S. Gabriel, *Ber.* 1885, **18**, 2438.

Of aliphatic compounds containing more than two nitro groups only a few will be discussed. Nitroform (trinitromethane), $CH(NO_2)_3$, is formed in small quantity by passing acetylene into a mixture of nitric and sulphuric acids,[1] or by the interaction of ethylene and fuming nitric acid.[2] In both these cases the yield is improved by adding a little mercuric nitrate, and in the latter case β-nitroethyl alcohol, $O_2N \cdot CH_2 \cdot CH_2OH$, the addition product of ethylene and nitric acid, has been isolated as an intermediate compound. Nitroform can be obtained from tetranitromethane which loses a nitro group under the action of potassium ethoxide or potassium hydroxide,[3] but the reaction is extremely dangerous, since sometimes violent explosions take place.[4] It can be prepared more conveniently by the action of potassium ferrocyanide on tetranitromethane.[5] The reaction proceeds quietly and quantitatively at room temperature if a saturated aqueous solution of potassium ferrocyanide is shaken with tetranitromethane; potassium nitrite and ferricyanide are formed and the potassium salt of nitroform crystallizes from the solution:

$$C(NO_2)_4 + 2K_4Fe(CN)_6 \longrightarrow C(NO_2)_2{:}NO \cdot OK + KNO_2 + 2K_3Fe(CN)_6.$$
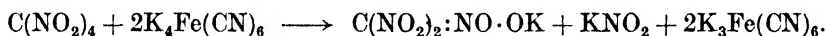
It can also be prepared with safety by shaking tetranitromethane with aqueous potassium hydroxide in the presence of glycerol.[6]

Nitroform is a colourless liquid which solidifies at 23°. In non-ionizing solvents its solutions are colourless, but its aqueous solution and its salts are yellow. In water it is strongly acidic: addition of hydrochloric acid causes the yellow colour to become paler. This suggests that it exists in two tautomeric forms, one colourless and not acidic and the other a yellow *aci*-form. If its potassium salt is treated with ice-cold concentrated sulphuric acid, a pale yellow oil is formed which solidifies on standing: the crystals after pressing on a porous plate melt at about 50°, but any attempt to purify them by recrystallization gives ordinary nitroform. These crystals are most probably the solid *aci*-form, while ordinary nitroform is the true nitro compound, $HC(NO_2)_3$. The mercuric salt of nitroform is a curious compound. It is a colourless solid easily soluble in organic solvents, notably in ether, and is even deliquescent in ether vapour.[7] Its solutions in ether, benzene, and chloroform are colourless, but solutions in the alcohols and aliphatic ketones are pale yellow. In water and pyridine it is deep yellow. The silver salt of nitroform which has the composition $AgC(NO_2)_3,H_2O$, shows the remarkably low melting-

[1] K. J. P. Orton and P. V. McKie, *J.C.S.* 1920, **117**, 283.

[2] P. V. McKie, ibid. 1927, 962.

[3] A. Hantzsch and A. Rinckenberger, *Ber.* 1899, **32**, 631.

[4] A. K. MacBeth, ibid. 1913, **46**, 2537, has given a vivid description of the destructive violence of such an explosion.

[5] F. D. Chattaway and J. M. Harrison, *J.C.S.* 1916, **109**, 171.

[6] A. K. MacBeth and W. B. Orr, ibid. 1932, 538.

[7] H. Ley and H. Kissel, *Ber.* 1899, **32**, 1365; H. Ley, ibid. 1905, **38**, 973.

point of 100°, and is readily soluble in ether.[1] There is the possibility of the formation of a chelate ring in these salts, e.g.

$$O_2N \cdot C \left\langle \begin{array}{c} \overset{O}{\underset{}{N}}{-}O \\ \underset{\underset{O}{\parallel}}{N}{=}O \end{array} \right\rangle Ag,$$
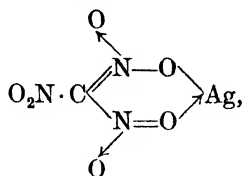
and this may be part of the explanation of their strange behaviour.

Tetranitromethane $C(NO_2)_4$ can be prepared in about 80 per cent. of the theoretical yield by allowing equimolecular amounts of nitric acid and acetic anhydride to react in the cold for several days.[2] It can also be obtained by heating with sulphuric acid the mixture obtained from the interaction of acetylene and nitric acid,[3] and by the nitration of nitroform.[4] It melts at 13° and boils without decomposition at 126°, is immiscible with water, and is stable when pure. Its mixtures with hydrocarbons, and especially aromatic hydrocarbons, can be detonated and are more sensitive to shock than nitroglycerine, and the violence of their explosion is very great.[5] The high oxygen content of the compound is clearly the reason for this behaviour. A marked yellow colour appears when tetranitromethane is mixed with an unsaturated or aromatic compound,[6] and hence it is sometimes used to test for the presence of double bonds in an unknown substance. The origin of the colour is not known.

As has been mentioned above, tetranitromethane reacts with concentrated potassium hydroxide or ethoxide to give almost quantitative yields of the potassium salt of nitroform and potassium nitrate. With more dilute potassium hydroxide in water, potassium nitrite and potassium carbonate are also formed; the reaction can take place in two ways[7] and the ratio

$$(A) \quad C(NO_2)_4 + 2KOH \longrightarrow KNO_3 + (O_2N)_2C:NO \cdot OK + H_2O$$

$$(B) \quad C(NO_2)_4 + 6KOH \longrightarrow 4KNO_2 + K_2CO_3 + 3H_2O$$
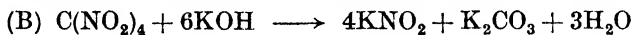
in which the two sets of products are formed depends on the strength of the alkali. In acid solution there is also an indication that tetranitromethane is hydrolysed to form nitrous acid, because Schmidt found that if a tertiary aromatic amine is added to such a solution, the p-nitroso derivative of the amine is formed. Schmidt draws the conclusion from these facts that tetranitromethane does not possess the structure implied by its name (XVII), but is the nitrous ester of trinitromethyl alcohol (XVIII), or rather an equilibrium mixture of these two compounds. He further

$$\text{XVII. } C(NO_2)_4 \qquad \text{XVIII. } (NO_2)_3C \cdot O \cdot NO$$
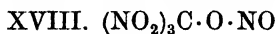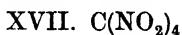
assumes that reaction (B) is characteristic of (XVIII), and reaction (A) of

[1] Hantzsch and Rinckenberger, loc. cit.
[2] F. D. Chattaway, *J.C.S.* 1910, **97**, 2099.   [3] Orton and McKie, loc. cit.
[4] A. Hantzsch, *Ber.* 1906, **39**, 2479.
[5] A. Stettbacher, *Z. ges. Schiess- u. Sprengstoffw.* 1930, **25**, 439.
[6] A. Werner, *Ber.* 1909, **42**, 4324.   [7] E. Schmidt, *Ber.* 1919, **52**, 400.

(XVII), and that the position of equilibrium alters with the strength of the hydrolysing alkali.

Such conclusions are very unlikely, and it is more probable that the reactions (A) and (B) are two modes of hydrolysis of one and the same compound, which has the structure (XVII). There is, however, a powerful argument which shows that, in solution in carbon tetrachloride, tetranitromethane contains four nitro groups. In that solvent (benzene cannot be used, because tetranitromethane forms an intensely yellow molecular compound with it) the electric moment of tetranitromethane is zero,[1] which can only be explained by accepting structure (XVII), or by saying that by chance the constituent moments of the molecule (XVIII), when added vectorially, cancel out. The latter explanation is shown to be untrue because the constituent moments can be obtained to a first approximation from measurements of nitromethane ($\mu = 3 \cdot 15$ D) and amyl nitrite ($\mu = 2 \cdot 27$ D) and the calculated moment for the molecule (XVIII) is $0 \cdot 8$ D, a value which is much greater than the limits of error in the measurements with tetranitromethane.

The ease with which a nitro group is split off from the compound makes it possible to use it as a nitrating agent.[2] Thus dimethyl-p-toluidine reacts with tetranitromethane in alcoholic solution to give m-nitrodimethyl-p-toluidine. Other compounds which are readily nitrated and are not themselves basic, such as phenols, can be nitrated in a similar way if pyridine is added. This is the only method known for introducing a nitro group directly into an aromatic nucleus in a non-acid solution. Tetranitromethane can also be used as a nitrosating agent, because it reacts with tertiary aromatic bases in the presence of pyridine to give the N-nitroso compound of the corresponding secondary amine, e.g. from dimethylaniline $\phi \cdot NMe_2$, N-nitrosomonomethylaniline, $\phi \cdot NMe \cdot NO$, is obtained.

The low boiling-point of tetranitromethane is remarkable. Nitromethane boils at 101°: dinitromethane is too unstable to be distilled under atmospheric pressure, but 1,1-dinitroethane, $CH_3 \cdot CH(NO_2)_2$, boils at 185°; yet in spite of its large molecular weight, tetranitromethane boils at 126°. The high boiling-points of the nitro-compounds in general are largely due, as we have seen, to the large electric moments of their molecules. Tetranitromethane has, it is true, no such moment, but this is due to the balancing of the large moments of the NO_2 groups against one another, and we might expect the high polarity of the individual groups to raise the boiling-point. It would seem that the close-packed structure of the $C(NO_2)_4$ molecule, with its eight negative oxygen atoms surrounding the CN_4 complex, makes any electrostatic association of the NO_2 groups impossible, so that the work of separation is less than in a dinitro compound.

[1] A. Weissberger and R. Sängewald, *Ber.* 1932, **65**, 701.
[2] E. Schmidt and H. Fischer, *Ber.* 1920, **53**, 1529, 1537.

AROMATIC NITRO COMPOUNDS

The aromatic nitro compounds are of much greater importance for preparative purposes and in industry than the aliphatic. The latter are for the most part difficult to obtain, while the former are in the majority of cases easily prepared by direct nitration and serve as intermediates in the preparation of a vast number of substances both in the laboratory and in chemical industry. Some of them are themselves of commercial importance, especially the polynitro compounds which are used as explosives.

The method which is almost always used for the preparation of aromatic nitro compounds is the action of nitric acid, or sometimes one of its derivatives, on an aromatic compound whereby a hydrogen atom attached to the nucleus is replaced by the nitro group. The reaction is of a different nature from the direct nitration of aliphatic compounds which has been discussed above (see p. 228); the latter are usually best nitrated with dilute nitric acid at temperatures above 100°, while aromatic compounds usually undergo nitration with concentrated nitric acid at lower temperatures. In general the aromatic compounds can be nitrated much more easily than the aliphatic, but it should be remembered that the difference is mainly one of conditions. Hexane can be nitrated with 13 per cent. nitric acid at 130°, under which conditions benzene is unattacked, and under the right conditions toluene can be nitrated, not in the nucleus but in the side chain, to give phenylnitromethane. The direct nitration of an aromatic compound was first carried out by Mitscherlich in 1834, when he obtained nitrobenzene by the action of fuming nitric acid on benzene.

Nitration may be effected in many different ways, and the choice between them depends on the compound to be nitrated; mention can be made here only of the more important methods.[1] Dilute nitric acid is rarely used except in the case of a compound which nitrates very readily, when it is desired to avoid the formation of polynitro compounds. Thus dilute nitric acid is used for the mononitration of phenol, since the strong acid gives the trinitro derivative, picric acid. Hot dilute nitric acid acts chiefly as an oxidizing agent. Concentrated and fuming nitric acids are sometimes used, particularly for the nitration of polycyclic compounds such as phenanthraquinone.[2]

The most commonly used nitrating agent is a mixture of concentrated or fuming nitric acid and concentrated sulphuric acid. The sulphuric acid appears to be of value in the process of nitration for a number of reasons. Firstly, it combines with the water produced during the reaction and so virtually prevents the dilution of the nitric acid; secondly, concentrated sulphuric acid possesses the power of dissolving nearly all organic substances, and this is possibly its most important function; thirdly, it has a marked effect in diminishing the oxidizing action of the nitric acid, which

[1] A more complete discussion will be found in Houben-Weyl, *Die Methoden der organischen Chemie*, Leipzig, 1924, vol. iv, p. 102 et seq.

[2] J. Schmidt and O. Spoun, *Ber.* 1922, **55**, 1199.

is most apparent at higher temperatures. Another occasional function of the sulphuric acid is to produce sulphonic acids, the sulphonic acid groups of which are subsequently replaced by nitro groups, thus regulating the entry of NO_2; e.g. in the preparation of picric acid from phenol in the usual way in the laboratory, phenol-2,4-disulphonic acid is first produced, and this is directly converted by the action of the nitric acid into picric acid; another example is the conversion of α-naphthol-2,4-disulphonic acid into 2,4-dinitro-α-naphthol (Martius Yellow).

The presence of sulphuric acid, it should be noted, has sometimes a considerable influence on the position taken up by the entering nitro-group, and this is particularly noticeable in the nitration of the acyl or alkyl derivatives of aromatic amino-compounds, when, in presence of concentrated sulphuric acid, the nitro group tends to enter the meta position with respect to the original amino group and not the usual ortho or para position. This effect is undoubtedly due to salt formation by the nitrogen atom (see p. 69).[1]

The dynamics of nitration in sulphuric acid have been investigated by H. Martinsen.[2] He used a solution of the aromatic compounds and nitric acid in equivalent quantities (from half to tenth normal) in sulphuric acid, and measured the progress of the reaction by extracting the nitro compound, or by determining the amount of free nitric acid remaining. He found the velocity to be proportional to the product of the concentration of the nitric acid and the aromatic compound. Nitrous acid appeared to have no catalytic effect, but the strength of the sulphuric acid has a great effect on the velocity, which reaches a maximum for an acid of the composition $H_2SO_4,0\cdot7\,H_2O$. The extent of this influence varies with the nature of the substituent already present in the nucleus, being especially high with the carboxylic and sulphonic acids.

A modification of the usual nitric-sulphuric acid mixture is to use concentrated sulphuric acid and solid potassium nitrate in those cases where nitration takes place with difficulty, e.g. the nitration of benzoic acid to m-nitrobenzoic acid. This mixture may also be used to introduce a number of nitro groups; o- and p-nitraniline yield picramide; aniline yields 2,3,4,6-tetranitroaniline. Difficult nitrations may sometimes be effected by a mixture of nitric acid and fuming sulphuric acid; for example, chlorobenzene cannot be nitrated beyond 2,4-dinitrochlorobenzene with nitric and sulphuric acids, but in the presence of fuming sulphuric acid 2,4,6-trinitrochlorobenzene is formed.

Easily substituted substances such as phenol ethers, hydroxy-aldehydes and their ethers, and acyl derivatives of bases are frequently nitrated by nitric acid in acetic acid solution in the cold. The acetic acid is sometimes replaced by acetic anhydride; the mixture probably contains some acetyl nitrate, $CH_3 \cdot CO \cdot O \cdot NO_2$, which is itself a powerful nitrating agent;[3]

[1] See also O. L. Brady, J. N. E. Day, and W. J. W. Rolt, *J.C.S.*, 1922, **121**, 526.
[2] *Z. phys. Chem.* 1905, **50**, 385; 1907, **59**, 605.
[3] A. Pictet and E. Khotinsky, *Ber.* 1907, **40**, 1163.

nitration of acetanilide with this mixture gives chiefly o-nitroacetanilide, while with nitric acid in acetic acid the product is the p-derivative. This tendency to give o-nitro derivatives is characteristic of acetyl nitrate itself, and also of benzoyl nitrate, $\phi \cdot CO \cdot O \cdot NO_2$, which is a powerful nitrating agent when dissolved in carbon tetrachloride or chloroform.[1]

Ethyl nitrate reacts with benzene and toluene in presence of aluminium chloride to give nitrobenzene and o- and p-nitrotoluene; it reacts as a much more vigorous nitrating agent in concentrated sulphuric acid at $-5°$, converting, for example, carbazole into 1,3,6,8-tetranitrocarbazole.[2] It is chiefly used, however, for replacing a hydrogen in a reactive methylene group by NO_2 under the influence of sodium ethoxide (see pp. 8 and 230).

Nitrous acid, prepared in situ from sodium nitrite and dilute sulphuric acid, may be used as a mild nitrating agent; salicylic acid gives 5-nitro-salicylic acid. Nitrous fumes from the decomposition of a nitrite with acid when passed into an ethereal solution of vanillin or guaiacol[3] gives 6-nitrovanillin or 2,4-dinitroguaiacol. The mechanism of these nitrations with nitrous acid and with nitrous fumes is certainly complicated; it may involve as a first stage the formation of a nitroso compound which is oxidized by oxides of nitrogen to the nitro compound. Other nitrating agents which have been employed in the aromatic series are diacetyl-orthonitric acid (p. 12) and tetranitromethane (p. 247).

During the process of nitration the entering nitro group may replace an atom or group other than hydrogen. Mention has already been made of the replacement of the sulphonic acid grouping; replacement of halogen in the polyhalogen phenols has been observed in a few cases.[4] Even alkyl radicals occasionally suffer replacement, as in the nitration of p-cymene, $CH_3 \cdot C_6H_4 \cdot CH(CH_3)_2$, which can lead to 2,4-dinitrotoluene;[5] the elimination of the carboxyl group or the aldehyde group occasionally occurs, e.g. the nitration of 2,4-dihydroxybenzoic acid gives mainly 2,4,6-trinitro-resorcinol (styphnic acid).[6] It may also be noted that nitric acid not infrequently reacts merely as an oxidizing agent, as in the oxidation of naphthalene to phthalic acid and pyrogallol trimethyl ether to 2,6-dimethoxy-p-benzoquinone.

The ease of nitration depends upon the nature of the group or groups already attached to the aromatic nucleus. In general, it may be said that those groups which direct the entering substituent into the ortho and para positions (e.g. OH, OAlk, CH_3, $NH \cdot CO \cdot CH_3$, &c.) facilitate the entry of the nitro group, although the halogens, which belong to the ortho-para-directing groups, appear to have but little effect on the ease of nitration.

[1] F. E. Francis, J.C.S. 1906, 89, 1; Ber. 1906, 39, 3798.

[2] H. Raudnitz and H. Böhm, ibid. 1927, 60, 738.

[3] W. Baker and R. Robinson, J.C.S. 1929, 156.

[4] L. C. Raiford and F. W. Heyl, Amer. Chem. J. 1910, 43, 393.

[5] J. Alfthan, Ber. 1920, 53, 78.

[6] For a summary of these displacements see M. P. de Lange, Rec. trav. chim. 1926, 45, 19.

The meta-directing substituents, on the other hand, make nitration take place less readily (compare the nitration of phenol and nitrobenzene). The whole problem of substitution in the benzene nucleus, including the position and ease of entry of a substituent into mono- and poly-substituted benzenes, the relative amounts of ortho-, meta-, and para-isomers produced, &c., is too large to be discussed here, and, further, since it is obviously connected not merely with nitration but with the entry of substituents in general, it cannot properly find a place in a book dealing with the organic chemistry of nitrogen compounds. Reference may be made, however, to a concise account of the modern electronic conception of substitution in the benzene nucleus by R. Robinson,[1] and to the work of L. E. Sutton[2] on the connexion between the electric moments of groups and their directing effect.

Indirect methods of preparing aromatic nitro compounds are of importance only in a few cases, and the only process of general application is the replacement of the amino group by NO_2 through the intermediate diazonium salt[3] which is discussed later (p. 407). In this way β-nitronaphthalene and p-dinitrobenzene (both inaccessible in quantity by direct nitration) may be prepared from β-naphthylamine and p-nitroaniline, respectively.

The mononitro derivatives of the aromatic hydrocarbons are for the most part yellowish or colourless solids which are nearly insoluble in water; a few only are liquid at room temperature. They are volatile in steam, and generally boil without decomposition at high temperatures.

	Melting-point	Boiling-point
Nitrobenzene	$+5 \cdot 8°$	$+209°$
m-Dinitrobenzene . . .	$91°$	$303°$
$symm$-Trinitrobenzene . .	$123°$	..
o-Nitrotoluene	$-9°$ ($-4°$, dimorph.)	$222°$
p-Nitrotoluene	$+51 \cdot 4°$	$238°$
$symm$-Trinitrotoluene . .	$81°$	..

The polynitro derivatives, on the other hand, are all solid, and when heated under atmospheric pressure sometimes explode with considerable violence. Trinitrotoluene is a well-known high explosive (p. 9).

They often have strong and characteristic smells. That of nitrobenzene is scarcely to be distinguished from that of benzaldehyde; p-nitrotoluene has a smell resembling that of hydrogen cyanide; and 2,4,6-trinitro-5-*tertiary*-butyl-meta-xylene is of commercial value since it possesses a powerful odour of musk.

In almost all cases the nitro group is firmly bound to the aromatic

[1] *J. Soc. Dyers and Colour., Jubilee Issue*, 1934, **50**, 65–76.

[2] *Proc. Roy. Soc.* 1931, A, **133**, 668.

[3] T. Sandmeyer, *Ber.* 1887, **20**, 1494; A. Hantzsch and J. W. Blagden, ibid. 1900, **33**, 2544.

nucleus, and does not undergo hydrolysis on treatment with either acids or alkalis (for exceptions see p. 257).

The *reduction of nitro compounds*, which has been examined in great detail, is by no means a simple process. A variety of products is obtained, according to the conditions of the reaction.

Speaking generally, the reduction proceeds in three ways, according as the solution is alkaline, neutral, or acid. In all cases the ultimate product, if the reducing agent is strong enough, is the primary amine.

If the nitro compound is reduced in alkaline solution and with not too vigorous a reducing agent, the main products are those formed by the condensation of two molecules of the nitro compound:

$$\phi \cdot NO_2 + O_2N \cdot \phi \longrightarrow \underset{\underset{O}{\downarrow}}{\phi \cdot N=N \cdot \phi} \longrightarrow \phi \cdot N=N \cdot \phi \longrightarrow \phi \cdot NH \cdot NH \cdot \phi$$

| Azoxy- | Azo- | Hydrazo-benzene. |

The earlier stages of the reduction proceed with ease. To obtain good yields of azoxybenzene it is sufficient to boil nitrobenzene with alcoholic potash or with sodium methoxide in methyl alcohol. The fate of the alcohol depends on the temperature used. At low temperatures it is oxidized to the aldehyde and at higher temperatures to the salt of the fatty acid.[1] With stronger reducing agents, such as zinc dust in excess, the reaction is very vigorous and the main product is hydrazobenzene.

Reduction in neutral solution leads to the N-arylhydroxylamine Ar·NHOH. It can be carried out by zinc dust or aluminium amalgam and water, and proceeds more rapidly and with better yield of the hydroxyl-amine in the presence of certain salts, notably ammonium chloride. The chief function of the salt is to act as a buffer and prevent the solution becoming too alkaline,[2] since in alkaline solution the phenylhydroxylamine undergoes further changes which are discussed below. Certain hydroxyl-amines are very prone to these further transformations; to obtain, for example, *m*-nitrophenylhydroxylamine by reduction of *m*-dinitrobenzene, more drastic steps, such as the addition of acetic acid, are necessary in order to keep down the concentration of the hydroxyl ions formed in the reduction.

Reduction in acid solution normally leads to the formation of the primary amine; but under special conditions, particularly with electro-lytic reduction, an amino-phenol is produced by the rearrangement of the intermediate hydroxylamine in the presence of the acid.

The causes which underlie the production of these various types of compounds under the different conditions, and particularly of the com-pounds with two benzene nuclei in alkaline solution, were most clearly revealed by F. Haber's study of the special case of electrolytic reduction.[3] The electrolytic method is peculiarly suitable for investigation; it can be

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[1] T. Rotarski, *Zent.* 1905, ii, 893.

[2] K. Brand and A. Modersohn, *J. pr. Chem.* 1928, **120**, 160.

[3] *Z. phys. Chem.* 1900, **32**, 193.

carried out both in acid and alkaline solution, and by varying the size and material of the electrodes and the current-density the reducing power can be varied within wide limits. The nitro compounds are not themselves electrolytes and the reduction is a secondary process carried out by the cathodic hydrogen. Its advantage for the present purpose is that it affords the same variation of results as would be produced chemically by reducing agents of greater or lesser strength without the complications which are necessarily introduced in the chemical method by changing the nature of the substances present. At the same time the reducing power of the hydrogen can be deduced from the cathode potential.

The first established product of the reduction of an aromatic nitro compound, whether in acid or alkaline solution, is the nitroso compound: $\phi \cdot NO_2 \longrightarrow \phi \cdot NO$. This is, however, much more readily reduced than the nitro body, as is shown by the fact that a much lower cathode potential is sufficient for the purpose, and it never attains more than a low concentration in the liquid. It has never been isolated, but its presence has been established in the following way. Nitrosobenzene is known to react in acid solution with hydroxylamine to give a benzene diazonium salt, which couples very readily with α-naphthylamine to form the dye-stuff benzene-azonaphthylamine. If nitrobenzene is electrolytically reduced in acid solution in the presence of both hydroxylamine and the naphthylamine, the dye-stuff is produced:

$$\phi \cdot NO + H_2NOH + HX \longrightarrow 2H_2O + \phi \cdot N_2X$$

$$\phi \cdot N_2X + C_{10}H_7 \cdot NH_2 \longrightarrow \phi \cdot N:N \cdot C_{10}H_6 \cdot NH_2, HX.$$
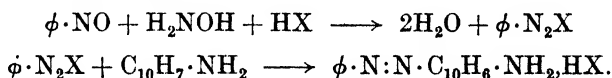
Under ordinary conditions the nitroso compound has only a transient existence and is rapidly reduced to the second main intermediate, the N-phenylhydroxylamine. This is an extremely reactive substance, and the main reason for the complexity of the reduction products under different conditions lies in the various reactions in which it can take part. In the presence of acids it can rearrange with the production of p-aminophenol:
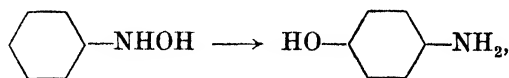
and hence this compound is found as a reduction product in acid, but never in alkaline solution. In alkaline solution phenylhydroxylamine condenses readily with nitrosobenzene, the first reduction product, to give azoxybenzene:

$$\phi \cdot NO + HONH \cdot \phi \longrightarrow \phi \cdot N:NO \cdot \phi.$$
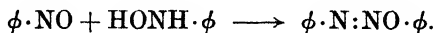
This reaction is important, as it is the main source of all the 'bimolecular' reduction products, and the amounts of these compounds formed depends on the velocity with which it takes place. This velocity has been measured in several cases and under various conditions by K. Brand and J. Mahr.[1]

[1] *J. pr. Chem.* 1931, **131**, 97; 1935, **142**, 161.

With nitrosobenzene and phenylhydroxylamine they found that, taking the velocity in neutral solution as unity, the velocity in presence of 0·005 M hydrochloric acid is 2 and if the acid is 0·01 M, 3, whereas with 0·0025 M potassium hydroxide it is of the order of 200, and with 0·005 M, 300. The preponderance of bimolecular products in alkaline reduction thus becomes intelligible. The rate of this coupling reaction to the azoxy compound also varies with the nature and position of the groups attached to the benzene nucleus, so that with certain substituents, such as a meta-nitro group, bimolecular products appear in neutral or very faintly acid solution. The amount of azoxy-compound formed by this route must clearly depend on the concentration of the nitroso compound: it is thus diminished by working with a high current-density, when the nitroso compound is rapidly reduced to the hydroxylamine.

In addition to this reaction there is another which leads to azoxybenzene. As has been mentioned above (see p. 163), phenylhydroxylamine changes spontaneously in alkaline solution into aniline and azoxybenzene by a process of mutual oxidation and reduction. This is a second source of bimolecular products.

$$3\phi \cdot NHOH \longrightarrow \phi \cdot NH_2 + \phi \cdot N{:}NO \cdot \phi + 2H_2O$$
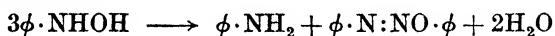
In acid solution, where these coupling reactions only take place to a small extent, the phenylhydroxylamine is reduced electrolytically to aniline, which is the chief product under these conditions.

Other products are also formed in addition to those mentioned so far, and they arise principally from secondary changes in the primary products. The more important are:

1. The azoxybenzene can be reduced electrolytically to hydrazo-benzene, but never to azobenzene. This affords a good laboratory method for preparing this compound, when lead electrodes are used.

2. The hydrazo compound can undergo further changes:

(a) In acid solution it may rearrange to benzidine (see p. 385).
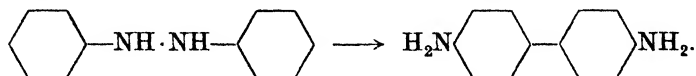
(b) In alkaline solution, and to a lesser extent in acid solution, it can be oxidized by the unattacked nitro compound to azobenzene, a reaction which appears to be the sole source of this compound in the reduction.

$$3\phi \cdot NH \cdot NH\phi + 2\phi \cdot NO_2 \longrightarrow 3H_2O + 3\phi \cdot N{:}N \cdot \phi + \phi \cdot N{:}NO \cdot \phi$$
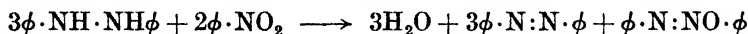
(c) It can be further reduced electrolytically to aniline, both in acid and alkaline solution.

These many reactions are summarized in the following scheme in which the vertical arrows indicate direct reduction by electrolytic hydrogen and the others secondary chemical reactions. The general scheme is the same whether the solution is acid or alkaline, but the relative amounts of the

various products are widely different in the two cases because of the effect on the velocities of the secondary chemical processes.[1]

$$\phi \cdot N:N \cdot \phi \xleftarrow{\quad \dfrac{\phi \cdot NH \cdot NH \cdot \phi}{Alkali} \quad} \phi \cdot NO_2$$

$$\phi \cdot N:N \cdot \phi \xleftarrow{\quad \dfrac{\phi \cdot NHOH}{Alkali} \quad} \phi \cdot NO$$

$$\phi \cdot NH \cdot NH \cdot \phi \qquad\qquad \phi \cdot NHOH \xrightarrow[Acid]{\quad} NH_2 \cdot C_6H_4 \cdot OH.$$

$$NH_2 \cdot C_6H_4 \cdot C_6H_4 \cdot NH_2 \qquad\qquad\qquad \longrightarrow \phi \cdot NH_2$$

(diagram annotations: $\phi \cdot NO_2$ / Alkali ; $\phi \cdot NO$ / Alkali ; Acid)
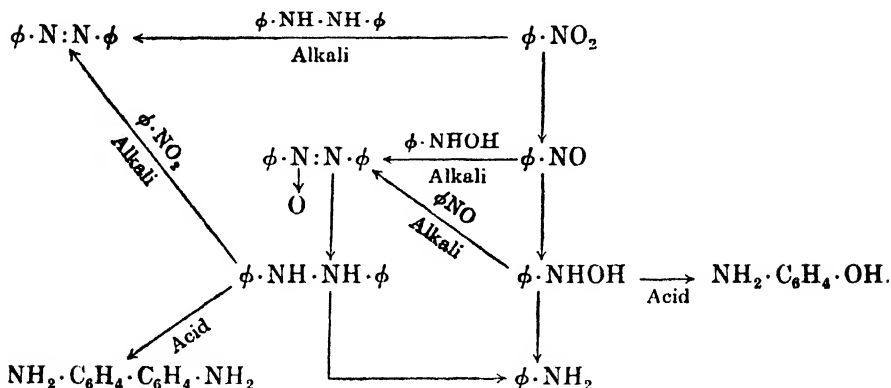
These facts established by Haber provide an explanation for the formation in the chemical reduction of nitro compounds of the various products which have been described above. They also throw light on certain other observations. Thus J. J. Blanksma[2] found that if nitrobenzene is reduced in strong hydrochloric acid at the boiling-point with a small quantity of tin, both ortho- and para-chloroaniline are formed. These clearly come from the phenylhydroxylamine which is reacting with the acid, as it is known to do (see p. 163), to give the chloroanilines. Again if nitrobenzene is reduced catalytically with hydrogen and platinum black in the presence of benzaldehyde, good yields of the N-phenyl ether of benzaldoxime are obtained;[3] this is the normal condensation of the phenylhydroxylamine and the benzaldehyde (see p. 163). A final example is the fact that in order to obtain an azo compound by direct reduction of a nitro compound, the solution must be alkaline and the amount of zinc dust used varies from case to case and must be very carefully controlled. The azo compound comes mainly from the interaction of the hydrazo compound and the unreduced nitro compound; thus the solution must be alkaline for any hydrazo compound to be formed and the reduction must not be too vigorous, or no unreduced nitro compound will remain.

The velocity of reduction of aromatic nitro compounds by chemical reagents has been studied in detail by H. Goldschmidt and his pupils.[4] The method was to determine by titration the concentration of the reducing agent at measured intervals of time. The stages were shown to be similar to those in electrolytic reduction. Reduction to the nitroso stage is the reaction which determines the velocity, the reduction of the nitroso compound to the hydroxylamine being very rapid, and that of the

[1] For a fuller account of Haber's work, see K. Brand, *Die elektrochemische Reduktion organischer Nitrokörper*, Stuttgart, 1908.

[2] *Rec. trav. chim.* 1906, **25**, 365.

[3] G. Vavon and M. Crajcinovic, *C.r.* 1928, **187**, 420.

[4] *Z. phys. Chem.* 1905, **48**, 435; 1906, **56**, 1, 385; 1910, **71**, 437.

hydroxylamine to the amine being always much more rapid than the first stage. With stannous chloride and hydrochloric acid the reaction is of the first order with respect to the stannous chloride and to the nitro compound, but the actual reducing agent appears to be the ion $[SnCl_3]^-$, because the rate is almost directly proportional to the concentration of hydrochloric acid, and is unaffected by replacing that acid by sodium chloride, which shows that the concentration of the chloride ion is the decisive factor. Similar results were obtained with stannous bromide and hydrobromic acid, except that in nearly all cases the rate of reduction is about eight times as fast. The effect of substituents in the benzene ring is shown very clearly in Goldschmidt's results. Some groups, such as the methyl and hydroxyl groups, diminish the rate of reduction and to about the same extent whatever their position in the ring. Other groups increase the rate, e.g. the carboxyl group, which is most effective as an accelerator when in the ortho position and has about the same effect in the meta as in the para. These results are in agreement with the inductive effects which these groups show in other reactions. When one group affects the reactivity of a second group attached to a benzene ring and the case is not one of steric hindrance, as with many ortho substituents, the cause of the effect may usually be looked for in the tendency of the first group to attract electrons to itself or to repel electrons from itself.[1] The reduction of the nitro to the nitroso group involves the withdrawal to the nitrogen atom of the two electrons which form the co-ordinate link. If, therefore, the nitrogen atom is made more positive, to use a somewhat loose phrase, the reduction will proceed more easily. An electron-attracting group will have this effect, while an electron-repelling group will tend to make the nitrogen atom more negative and will have the opposite effect. From their orientating effects in substitution, the carboxyl group is known to be electron-attracting and the methyl and hydroxyl groups to be electron-repelling, and thus their opposite effects on the ease of reduction of the nitro group in substituted nitrobenzenes becomes comprehensible.

The action of the amino group is especially interesting. Being weak bases, the nitroanilines are present in acid solution partly as such and partly in the ionic form $-NH_3^+$. The velocity of their reduction increases abnormally fast with the concentration of the acid. That it is the acid which causes this, is shown by the fact that addition of sodium chloride, though it increases the velocity of reduction by increasing the concentration of the $SnCl_3^-$ ion, does not do so to the same extent as the equivalent of hydrochloric acid. Hence it must be that the free base is reduced slowly and the kation more readily, because no other change in the state of the base is brought about simply by increasing the acid concentration. This is exactly what would be expected from the above considerations; the amino group is electron-repelling, but the $-NH_3^+$ group, in virtue of its charge, attracts electrons. There is a close parallel with the opposite

[1] R. Robinson, *J. Soc. Dyers and Colour., Jubilee Issue*, 1934, **50**, 65–76.

orientating effects of the uncharged and positively charged amino groups (see p. 69).

With stannous chloride in alkaline solution, it has been shown that the reducing agent is the ion $[SnO_2H]^-$. Allowing for this, the reaction is again bimolecular; the further stages proceed as in acid solution, but with much greater velocity.

Intimately connected with the reduction of the nitro group is the use of nitro compounds as oxidizing agents. For obvious reasons nitrobenzene is the only compound which has found many applications, and these are mostly technical. For operations on the laboratory scale nitrobenzene is usually not convenient owing to the number of different reduction products produced during the reaction from which the desired oxidation product is separated only with difficulty. On the commercial scale, however, these difficulties may be balanced by the relatively low cost of nitrobenzene and by the sale of the aniline.

Nitrobenzene is used in preparation of dyes of the rosaniline type, e.g. the oxidation of a mixture of aniline and toluidines (see p. 86); in the Skraup quinoline synthesis it is used to oxidize dihydroquinoline to quinoline (p. 544); it oxidizes tetrahydroquinoline to quinoline at the boiling-point, and will even oxidize piperidine to pyridine at 250–260°. Owing to the fact that nitrobenzene can act as an oxidizing agent in presence of aqueous solutions of alkali hydroxides, it may be used to oxidize substances containing free phenolic hydroxyl groups, whilst with most oxidizing agents these groups have first to be 'protected' in some way. A commercially important application of this is the oxidation of iso-eugenol, $HO(MeO) \cdot C_6H_3 \cdot CH : CH \cdot CH_3$, to vanillin,
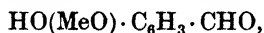
$$HO(MeO) \cdot C_6H_3 \cdot CHO,$$

by heating with nitrobenzene and aqueous sodium hydroxide; a similar use is the oxidation of acetovanillone to 4-hydroxy-3-methoxyphenyl-glyoxylic acid, $HO(MeO)C_6H_3 \cdot CO \cdot CH_3 \longrightarrow HO(MeO)C_6H_3 \cdot CO \cdot CO_2H$.[1] Mention may also be made of the conversion of o-nitrotoluene into anthranilic acid by heating with aqueous or alcoholic sodium hydroxide.[2]
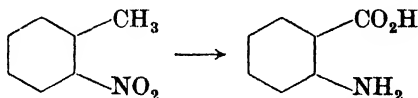
Reactivity of the Nitro group. The nitro groups may be exchanged indirectly for almost any other by reduction to the primary base and diazotization (see p. 404). A direct exchange is difficult, especially with the simple mononitro derivatives, but if there are several nitro groups present it can be effected more easily. Thus o- and p-, but not m-dinitro-benzene can have an NO_2 replaced by hydroxyl (with formation of potassium nitrite) by boiling with aqueous potassium hydroxide, by

[1] H. O. Mottern, *J. Amer. C. S.* 1934, **56**, 2107.
[2] L. Preuss and A. Binz, *Z. angew. Chem.* 1900, **13**, 385.

ethoxyl on treatment with alcoholic potassium hydroxide, and by NH_2 or $NH\phi$ with ammonia or aniline. A similar example of the activity of a nitro group is afforded by 1,2,3,5-tetranitrobenzene, which is prepared from ethyl picrate by conversion into picrylhydroxylamine and treatment with nitric acid:[1]

$$(O_2N)_3C_6H_2 \cdot OEt \longrightarrow (O_2N)_3C_6H_2 \cdot NHOH \longrightarrow (O_2N)_3C_6H_2 \cdot NO_2.$$
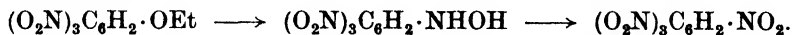
Although its method of formation shows that this substance is a true nitro compound and not a nitrite, it is readily hydrolysed to picric acid, and gives picramide with ammonia.

In the case of certain polynitro compounds a nitro group is easily replaceable by other radicals when the other nitro groups are in the meta position with respect to it; thus 1,3,5-trinitrobenzene is converted into 3,5-dinitroanisole by boiling with a solution of sodium methoxide in methyl alcohol:[2]
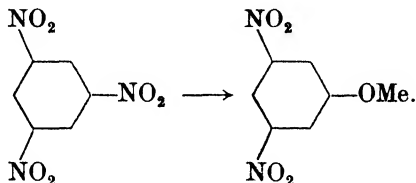
In the great majority of cases, however, this mobility of a nitro group is found when there is another nitro group in the ortho or para positions. The usual effect of a nitro group is to activate the meta position in a benzene derivative, and not the ortho or para. These apparently conflicting results are explained by the electronic theory of substitution in the benzene nucleus,[3] and are due to the fact that whilst, for example, nitrobenzene acts as a meta directing group towards the usual kationoid reagents (HNO_3, H_2SO_4, halogens, &c.) (the meta carbon atom, with a relative excess of electrons, uniting with the kationoid reagent), it must react as an ortho-para directing group towards anionoid reagents (NaOH, NH_3, NaOEt, &c.) (the ortho and para carbon atoms, which possess a deficit of electrons, uniting with the anionoid reagent). These reactions are for the most part exchange reactions, such as the hydrolysis of the nitro compounds mentioned above, but examples of the replacement of hydrogen of the benzene nucleus are known. Nitrobenzene when heated with solid potassium hydroxide yields o-nitrophenol,[4] and when treated with piperidine and sodamide yields N-p-nitrophenylpiperidine.[5] Exactly analogous is the well-known mobility conferred upon halogen atoms by the presence of nitro groups in the ortho and para positions; ortho- and para-nitro-halogen compounds are hydrolysed by boiling with alkali hydroxide, the 2,4-dinitro-halogen compounds are more reactive still and will even condense with sodio-malonic ester, while 2,4,6-trinitro-

[1] W. Borsche, *Ber.* 1923, **56**, 1942.
[2] C. A. Lobry de Bruyn, *Rec. trav. chim.* 1890, **9**, 208.
[3] See R. Robinson, loc. cit.   [4] A. Wohl, *Ber.* 1899, **32**, 3486; 1901, **34**, 2444.
[5] W. Bradley and R. Robinson, *J.C.S.* 1932, 1254.

chlorobenzene (picryl chloride) behaves towards alkalis and ammonia as an acid chloride. Similar again is the reactivity exhibited by the 2,4-dinitrophenol ethers, which are readily hydrolysed by alkalis, converted into 2,4-dinitroaniline by the action of ammonia, and suffer exchange of alkyl groups by treatment with different sodium alkoxides, so that their reactions resemble those of a carboxylic ester rather than a phenolic ether.

Aromatic Nitro Compounds and Alkalis

In aromatic nitro compounds the nitro group is of necessity attached to a tertiary carbon atom, and hence they cannot react with bases to form salts in which the anion has the *aci*-nitro structure, as happens with the primary and secondary aliphatic nitro compounds. Nevertheless, the aromatic nitro compounds, and especially those containing more than one nitro group, show a remarkably interesting behaviour towards alkalis. Mononitro derivatives, such as nitrobenzene, are not affected by alkalis in the cold. Ordinary commercial nitrobenzene, it is true, gives a red colour if a drop of caustic potash is added to its alcoholic solution, but this is due to the presence of 2,4-dinitrothiophene formed during the nitration from thiophene in the original benzene. Pure nitrobenzene gives no such colour and this fact can be used to detect thiophene in a sample of benzene; a few drops of the sample can be nitrated in a test-tube and the product, after washing, tested in alcoholic solution with a drop of concentrated potassium hydroxide solution.

The di- and tri-nitro derivatives, on the other hand, give colours with alkali even when they are pure; thus 1,3,5-trinitrobenzene gives a red colour and trinitromesitylene (1,3,5-trinitro-2,4,6-trimethylbenzene) is soluble in aqueous caustic alkalis to give a red solution. Compounds of the nature of salts must be formed, but they cannot arise by replacement of a hydrogen atom attached to the nucleus, since there is no such hydrogen atom in trinitromesitylene, and further C. A. Lobry de Bruyn[1] has shown that metallic potassium does not react with trinitromesitylene. The salts must be formed by the addition of a molecule of the alkali hydroxide or alkoxide to the polynitro compound. This is clearly shown by the composition of those which have been isolated; when trinitrobenzene, for example, in methyl alcohol is treated with its equivalent of potassium hydroxide in concentrated aqueous solution, red crystals separate which are somewhat explosive and regenerate trinitrobenzene on treatment with acids; analysis shows that their composition corresponds with the formula[2]

$$C_6H_3(NO_2)_3, CH_3OK, H_2O.$$
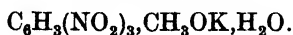
In one case, that of 2,4,6-trinitrotoluene, Hantzsch and Kissel were able to isolate the acid from which the salts are derived by acidifying the potassium salt at a low temperature; its composition and molecular weight could be determined and corresponded to an addition compound of

[1] *Rec. trav. chim.* 1895, **14**, 89.

[2] Lobry de Bruyn, loc. cit.; A. Hantzsch and H. Kissel, *Ber.* 1899, **32**, 3137.

trinitrotoluene and methyl alcohol. This 'nitronic' acid is not very stable, but an acetyl derivative can be prepared from it by the action of acetyl chloride, which is an indication that it contains a hydroxyl group. Hantzsch's original suggestion was that the addition took place to one of the nitro groups and he wrote the formula of the potassium salt of trinitro-

benzene as $(O_2N)_2C_6H_3 \cdot N \overset{O}{\underset{OK}{<}}$. J. Meisenheimer[1] objected to this view on the ground that the profound colour change on salt formation indicates that the aromatic ring is involved; he suggested that the alkoxy group is attached not to a nitrogen atom, but to a carbon atom of the benzene ring, as in the formula (I).
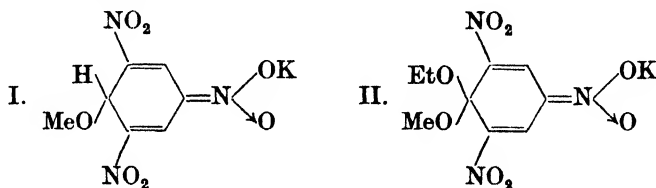
He was able to find support for this suggestion in an ingenious way. If on the one hand trinitro-anisole combines with potassium ethylate, and on the other trinitrophenetole combines with potassium methylate, the products on Hantzsch's view should be different. On Meisenheimer's view the alkoxy group attaches itself to a carbon atom in the para position to a nitro group, i.e. either to one of the CH groups or to the C·OAlk. If the latter is true the structure of the product will be the same in both cases, namely (II). Experiment showed that the two products were in fact identical, and this is valuable evidence as to the structure of the compounds.

Meisenheimer's formula, however, cannot be considered as completely satisfactory; it does not take into account the fact that more than one nitro group must be attached to the nucleus for this type of salt formation to take place, nor does it offer any explanation of the deep colour of the salts. It is evident that the stability of the compounds and their colour has something to do with all the nitro groups and not only with one. The compounds in which the salt formation occurs are those in which two or more nitro groups are in the meta position to one another. The anion from such a compound can be written in as many separate formulae as there are nitro groups: e.g. the anion of the addition product of potassium methylate and trinitrobenzene can be written in the three forms
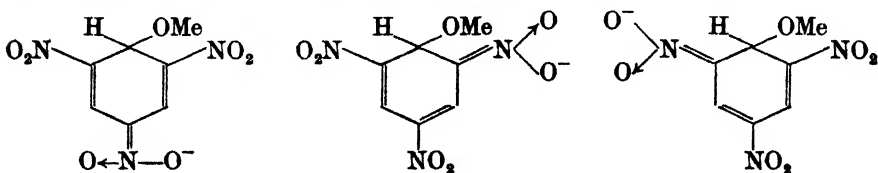
[1] *Annalen*, 1902, **323**, 205.

and these formulae do not differ in the positions of the constituent atoms, but only in the kinds of valencies uniting the atoms. Hence the anion is almost certainly a resonance-hybrid of all three formulae, a view which offers the best explanation of the necessity for the presence of more than one nitro group; the extra stability arising from the resonance will account for the formation of the compounds, and their colour may well be due to the resonance between the quinonoid systems in much the same way as in the triphenylmethane dyes.

Molecular Complexes with Hydrocarbons and Bases

The existence has long been recognized of a large group of crystalline complexes containing in stoichiometric proportions polynitro-aromatic substances such as trinitrobenzene or picric acid and aromatic hydrocarbons and bases and their derivatives.[1] These complexes are, for the most part, unstable, and, although they can generally be prepared by crystallization from one solvent, they are often decomposed by another. The conditions under which they can be isolated from solution and the general question of their stability towards solvents has been discussed by O. Dimroth.[2] van't Hoff deduced thermodynamically a general relation between solubilities and equilibrium concentrations which Dimroth first applied to tautomeric systems, $A \rightleftharpoons B$, and later extended to the general case of complex formation $A + B \rightleftharpoons C$ $(C = AB)$. The affinity of the process solid A + solid $B \rightarrow$ solid complex C is given by $RT \ln \dfrac{S_A \cdot S_B}{C_A \cdot C_B}$ per gram molecule, where S_A and S_B are the solubilities of A and B and C_A and C_B are the concentrations of A and B in a solution in equilibrium with solid complex C. It follows that $\dfrac{S_A \cdot S_B}{C_A \cdot C_B} = e^{\frac{A}{RT}} = G$ (i), a constant independent of the solvent at constant temperature. Further, if B is less soluble than A, the maximum value for C_B in any solvent is S_B, and since $C_A = C_B$, the maximum value for $\dfrac{S_A}{S_B}$ is G. That is to say, if the complex is to be stable in a solvent, the ratio of the solubility of the more soluble to that of the less soluble component must be less than G. Knowing S_A, G can be determined by finding C_A in a solvent that is not only in equilibrium with solid complex but is also saturated with B, for then $C_B = S_B$ in equation (i) above. Dimroth and Bamberger tested these conclusions for the complex formed between anthracene and picric acid. G was found at $25 \cdot 14°$ C. from experiments in five different solvents to be $2 \cdot 32$ (mean of values from $2 \cdot 1$ to $2 \cdot 47$), and tabulated below are given the ratios of the solubilities of anthracene and picric acid in the various

[1] J. J. Sudborough, *J.C.S.* 1901, **79**, 522; 1910, **97**, 773; A. Werner, *Ber.* 1909, **42**, 4324; P. Pfeiffer, *Organische Molekülverbindungen*, Stuttgart, 1927, p. 335 et seq.

[2] O. Dimroth and C. Bamberger, *Annalen*, 1924, **438**, 67.

solvents and the effect of the solvents on the stability of the anthracene
—picric acid complex.

Solvent	$\dfrac{S_{\text{anthracene}}}{S_{\text{picric acid}}}$	$\dfrac{S_{\text{picric acid}}}{S_{\text{anthracene}}}$	Effect of solvent
Carbon tetrachloride	7·7	0·13	picric acid separates
Ligroin . . .	1·85	0·54	no decomposition
Ether . . .	0·5	2·0	,, ,,
Alcohol . . .	0·036	28	anthracene separates
Water . . .	very small	very large	,, ,,

The magnitude of the constant G is a measure of the stability of the
solid complex, and Bamberger and Dimroth's measurements lead, for
a series of picrates, to the following relative order of increasing stability:
benzene $<$ fluorene $<$ anthracene $<$ indene $<$ phenanthrene $<$ naph-
thalene $<$ acenaphthene $<$ α-methyl naphthalene $<$ β-methyl naph-
thalene.

There is abundant evidence that interaction of some kind occurs in
solution between polynitro compounds and aromatic hydrocarbons and
bases. Thus in most cases a colour change, often very pronounced, is
observed. Further, R. Behrend[1] showed that the solubility of anthracene
in alcohol is increased by picric acid and, assuming an equilibrium in
solution to which the law of mass action could be applied, found a dis-
sociation constant $\dfrac{C_{\text{complex}}}{C_A \cdot C_B}$ of 4·7–5·7 at 25° C., a result confirmed by
Bamberger and Dimroth.[2] Similarly F. S. Brown[3] found that the depres-
sion of the freezing-point of nitrobenzene by mixtures of naphthalene
and picric acid could be interpreted to give a dissociation constant of 0·23
and a heat of formation of 2,080 cals., in good agreement with the value
2,150 cals. obtained by J. N. Brönsted[4] from determinations of E.M.F.
in the system naphthalene—picric acid—KCl—HCl—H_2O.

It must, however, be noted that the effects described above may be
due in part or even in their entirety to intermolecular forces that are not
chemical. The nitro group is highly polar and aromatic substances are
polarizable. It may, therefore, well be that equilibrium constants derived
from alterations in the solubility of a polar solute by the addition of a
polarizable second component have no more real significance than the
apparent dissociation constant of a strong electrolyte calculated from the
depression of the freezing-point of water. An attempt to meet this
difficulty has been made by T. S. Moore, F. Shepherd, and E. Goodall,[5]
who measured the effect of the presence of a number of substituted
aromatic hydrocarbons and bases on the partition of picric acid between
chloroform and water. In all cases an increase of the solubility of the
picric acid in the chloroform was observed. To ascertain the 'normal'

[1] Z. phys. Chem. 1894, 15, 183.   [2] Loc. cit.   [3] J.C.S. 1925, 127, 345.
[4] Z. phys. Chem. 1911, 78, 284.   [5] J.C.S. 1931, 1447.

effect of a second component with which picric acid could not be expected to combine chemically, substances such as hexane and carbon tetrachloride were added to the water, picric acid, chloroform system and found to depress the solubility of the acid in the chloroform layer. They therefore conclude that the increased miscibility of the picric acid caused by the presence of aromatic substances is mainly due to chemical interaction in the liquid phase and derive a series of equilibrium constants that give a stability series agreeing with that of Bamberger and Dimroth, and extend it to include nitro- and halogenobenzenes.

The problem of the structure of the polynitro complexes is a difficult one, owing to the fact that their instability has hitherto made it impossible to distinguish any chemical properties peculiar to the complexes themselves. It is practically certain, however, that the nitro group is a point of attachment, since they can be obtained with nitro compounds such as trinitromesitylene and trinitrotrichlorobenzene. The fact that hexamethylbenzene forms a well-defined compound with *symm*-trinitrobenzene rules out the possibility of co-ordination to nuclear hydrogen atoms. G. M. Bennett and G. H. Willis[1] suggest that the union must be through a single nitro group, any others present in the same molecule having an indirect reinforcing effect. In support of this they point out that, although molecular compounds of mononitrobenzenes (excepting nitrophenols) are practically unknown, the substances (I) and (II), in which the nitro group is reinforced by other electron-attracting groups, do yield such complexes.

$$\text{I.} \quad \underset{NO_2}{\overset{MeO_2C \qquad CO_2Me}{\bigcirc}} \qquad \text{II.} \quad \underset{NO_2}{\overset{ClO_2S \qquad SO_2Cl}{\bigcirc}}$$
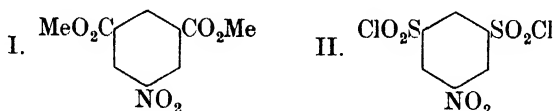
The occurrence of benzene and of ethylene in metal co-ordination compounds such as $Ni(CN)_2 \cdot NH_3 \cdot C_6H_6$ and $PtCl_2 \cdot NH_3 \cdot C_2H_4$ suggests the possibility of co-valency formation by ethylene and benzene acting as electron donors. This conception is the basis of Bennett and Willis's formulation of the interaction of the nitro group with bases and aromatic substances. They suppose that the nitro group functions in the 'kationoid' form $-\overset{+}{N}\overset{O^-}{\underset{O}{\diagdown}}$, attachment to an amine taking place by means of the 'lone pair' of electrons on the nitrogen atom of the latter: $Ar-\overset{O}{\underset{O}{\overset{-}{\diagdown}}}\overset{+}{N}\leftarrow NR_3$. Combination with hydrocarbons is regarded as occurring with one ethylenic bond in the polarized form $-\overset{-}{CH}-\overset{+}{CH}-$ to give

$$Ar-\overset{O}{\underset{\;}{\overset{\diagup O^-}{N}}}\leftarrow\overset{|}{CH}-\overset{+}{\underset{|}{CH}}.$$
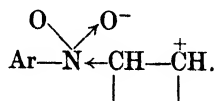
[1] *J.C.S.* 1928, 2305.

G. Briegleb[1] has suggested that the polynitro complexes are the products of electrostatic interaction between the polar nitro groups and electric dipoles induced or already present in aromatic hydrocarbons and bases. On this hypothesis he is able to compute heats of interaction of the order of 2 kcals. per gm. mol. for assumed intermolecular distances of 2 A. As the experimentally found heats of interaction are about 1–5 kcals. per gm. mol. and as the law of force between the polarizing and polarized molecules is according to the inverse sixth power of the intermolecular distance, the inference is that the interacting molecules cannot get as close together as is required for ordinary chemical bond formation (1–2 A). This conclusion is in agreement with the crystallographic evidence of H. M. Powell and G. Huse,[2] who show that in the well-defined crystalline compound of picryl chloride with hexamethylbenzene, there is no intermolecular distance comparable with a normal bond length.

Dipole aggregates can be set up by electrostatic interaction either side by side, $\rightleftarrows$, or end to end, $\longrightarrow \longrightarrow$. The permanent dipoles of nitro groups might be expected to interact according to the first of these modes. Complex formation between nitro compounds is known (e.g. between di- and tri-nitrobenzenes) and takes place without colour change.[3] It has been suggested that the colour-producing interactions such as take place between trinitrobenzene and naphthalene or naphthylamine, are of the end-to-end type and that they may be regarded as incipient oxidation-reduction (base-acid) processes. Thus when an amino group approaches a nitro group, it is supposed that the induced dipole effect results in a projection of electrons from the —NH_2 (oxidation) towards the —NO_2 group, in which a recession of electrons occurs (reduction) from the oxygen atoms towards the nitrogen and into an aromatic nucleus, if present, (I).[4]
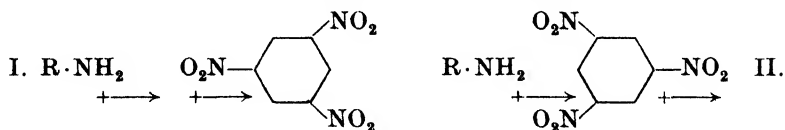
The presence of an aromatic nucleus in the nitro compound is not essential to the production of colour, as is shown by the fact that tetranitromethane gives colours on admixture with aromatic substances and bases; no solid complexes of tetranitromethane are known, however.

The recession, suggested above, of electrons from oxygen to nitrogen in the nitro group is in the direction opposite to that in which polarization is generally supposed to take place. It may, moreover, be noted that the action of powerful bases such as OH^- and OEt^- on such nitro compounds as trinitrobenzene and trinitroanisole produces colours which resemble closely those produced in 'nitro-body complex' formation and which are almost certainly caused by definite molecular structures produced as the

[1] *Ahrens' Sammlung*, 1937, **37**, 1–308.   [2] *Nature*, 1939, **144**, 77.

[3] Moore, Shepherd, and Goodall, loc. cit.; D. Ll. Hammick, L. W. Andrew, and J. Hampson, *J.C.S.* 1932, 171.

[4] Hammick and Miss R. B. M. Yule, *J.C.S.* 1940, 1539; R. E. Gibson and O. H. Loeffler, *J. Amer. C. S.* 1940, **62**, 1324.

result of electron shifts from nitrogen to oxygen:
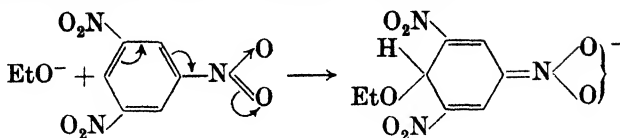
It may be that weaker bases (reducing agents) such as aromatic amines and hydrocarbons, though not sufficiently anionoid to carry through a complete reduction of the nitro group in the above sense, may nevertheless induce an incipient reduction capable of producing the observed colours, (II). That sufficient interaction to produce colour occurs during mere thermal impact is indicated by the fact that colourless 4,6,4′,6′-tetranitrodiphenyl gives yellow solutions in toluene. These components have so little tendency to 'compound' formation that on cooling they separate into two liquid layers.[1]   D. Ll. H.

Nitrophenols

The nitrophenols are usually obtained by the direct nitration of phenols with dilute nitric acid, as has already been mentioned. The reaction is not a simple interaction of nitric acid and the phenol but is extremely complicated in its mechanism. If the nitric acid has been carefully freed from nitrous acid, there is a period of induction before the reaction begins. With a trace of nitrous acid the reaction begins at once, and, within limits, with greater speed the larger the amount of nitrous acid. The suggestions which have been made to account for the importance of nitrous acid in the reaction can be divided into two groups. In the first the effect is attributed to an interaction between the nitrous and nitric acids. Thus A. Klemenc and R. Schöller[2] thought that nitric acid and nitrogen peroxide formed a complex of composition $NO_2,2HNO_3$ which was the actual nitrating agent, while A. Klemenc and L. Klima[3] suggested that nitric acid formed in the known equilibrium $3HNO_2 \rightleftharpoons HNO_3 + 2NO + H_2O$ is 'activated'. These rather vague ideas find little support from measurements of rate of reaction and contribute little towards any knowledge of the reaction mechanism.

The second group of suggestions is that in which the effect is attributed to an interaction between the nitrous acid and the phenol. It has frequently been suggested that the velocity of nitrosation of a phenol may be greater than that of nitration, and that, since nitrosophenol is known to be oxidized to a nitrophenol by nitric acid, the mechanism of nitration is that the phenol and nitrous acid interact to give a nitrosophenol which is then oxidized to the nitro compound.[4] Such a simple explanation is, however, manifestly untrue, because when phenol itself is nitrated the ortho- and para-nitrophenols are formed in equal quantity, while in its nitrosation more than 90 per cent. of the nitrosophenol is the para com-

[1] Hammick and G. Sixsmith, *J.C.S.* 1939, 972.

[2] *Z. anorg. Chem.* 1924, **141**, 231.   [3] Ibid. 1929, **179**, 379.

[4] Cf. A. L. Kartashev, *J. Russ. Phys. Chem. Soc.* 1930, **62**, 2129; *Zent.* 1931, ii. 707.

pound. The accurate study of the problem by measurement of reaction velocity is difficult because of the formation of by-products, but from the measurements available[1] it seems necessary to assume that in solution phenol and nitrous acid are in equilibrium with two addition complexes formed from them. If nothing but phenol and nitrous acid are present, there is a certain probability that one of these complexes loses water to form *p*-nitrosophenol and the other *o*-nitrosophenol, and since the ortho complex is present in smaller amount than the para, in nitrosation the yield of *o*-nitrosophenol is small. If nitric acid is present, the complexes are oxidized to nitrophenols, but the ortho complex much more rapidly than the para, so that, although only a little ortho complex is present in equilibrium with its components, the yield of *o*-nitrophenol is as large as that of *p*-nitrophenol. This explanation of Veibel's is based on a certain amount of experimental evidence: what it amounts to is the assumption of two different collision-complexes between phenol and nitrous acid which react at different rates with nitric acid.

Certain nitrophenols are most conveniently prepared by the oxidation of the nitrosophenols; thus 4-nitroresorcinol is produced from 4-nitroso-resorcinol (itself prepared from resorcinol, amyl nitrite, and alcoholic potash) by oxidation with hydrogen peroxide.[2] Other methods of preparation are the alkaline hydrolysis of the ortho- and para-nitrochloro- (or bromo-) benzenes and the corresponding amino-benzenes (see p. 73), the preparation of *m*-nitrophenol from *m*-nitraniline through the diazo reaction, the preparation of 2,4-dinitrophenol and picric acid by the oxidation of *m*-dinitrobenzene and of *symm*-trinitrobenzene, respectively, by means of potassium ferricyanide, and the direct formation of picric acid from benzene and nitric acid in presence of mercuric nitrate.[3]

The colours of the nitrophenols and their derivatives both in the solid state and in solution have been the subject of many investigations, especially by Hantzsch and his co-workers. Nevertheless, the whole question of the light absorption by these and other nitro compounds still remains obscure in many respects.[4] The more important facts may be summarized as follows. Many nitrophenols are nearly or quite colourless (*p*-nitrophenol, 2,4-dinitrophenol, &c.). Others, like *o*-nitrophenol, are distinctly coloured. Their colour is least in non-ionizing solvents; in water many give definitely coloured solutions, of which the colour becomes much more intense on the addition of alkali, and fades away on the addition of strong acid; the salts are all coloured.

Their normal ethers, prepared by the usual methods of alkylation, such as nitroanisole, $NO_2 \cdot C_6H_4 \cdot OCH_3$, and the alkyl picrates are colourless. A. Hantzsch and H. Gorke,[5] however, state that in certain cases

[1] S. Veibel, *Ber.* 1930, **63**, 1577, 1582, 2074; *Z. phys. Chem.* 1930, B, **10**, 22.

[2] W. Borsche and A. D. Berkhout, *Annalen*, 1903, **330**, 106.

[3] L. Vignon, *Bull. Soc. chim.* 1920, **27**, 547.

[4] See J. Eisenbrand and H. v. Halban, *Z. phys. Chem.* 1930, A, **146**, 30, 101, 110.

[5] *Ber.* 1906, **39**, 1073.

isomeric alkyl ethers can be prepared by treating the silver salts of the nitrophenols with an alkyl halide, using scrupulously pure and dry materials and with the rigid exclusion of all moisture. In this way red, unstable ethers were obtained from o-nitrophenol and from picric acid, the latter giving the better results, though even in this case the yield was only 1·5 per cent. and the red ether contained 10 per cent. of the ordinary ether. These unstable coloured ethers have only been isolated in the case of a few o-nitrophenols, and it is doubtful if they exist in the para and meta series. They are probably derived from an *aci*-nitro form of the nitrophenol, and their instability and ready hydrolysis may be compared with those of the esters of the *aci*-forms of aliphatic nitro compounds (see p. 236).
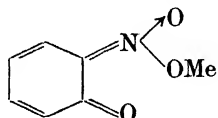
The salts of the o-, m-, and p-nitrophenols are all more deeply coloured than the phenols from which they are derived: the absorption bands of the free phenol shift towards the red when it becomes an anion. This phenomenon is a very general one, and is shown by many other groups of compounds, such as hydroxy ketones, and oximes of nitro-aldehydes. It is unnecessary to deduce from this shift that the anion and the undissociated nitrophenol have fundamentally different structures.[1] Not infrequently, however, a single nitrophenol gives rise to two differently coloured salts, yellow and red, with the same alkali. There appears to be little reason for the frequent attempts that have been made to relate these differently coloured salts with the isomeric ethers isolated by Hantzsch, since the differences in the salts appear to be confined to the solid state, being, in fact, usually associated with different amounts of water of crystallization.[2] There is no need, therefore, to postulate that the differently coloured salts are derived from isomeric forms of the nitrophenols themselves, as is probably the case with the ethers discussed above. Such an attempt, moreover, at once leads to difficulties, since although it is possible to formulate an *aci*-nitro form of o- or p-nitrophenol, e.g. (I) and (II), an *aci*-nitro form in the meta series (III) involves a meta-quinonoid structure,
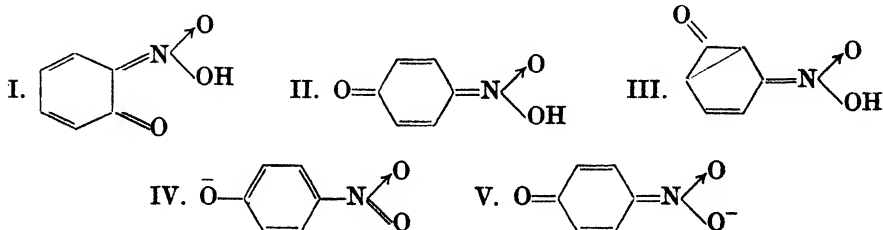
[1] E. C. C. Baly, W. B. Tuck, and E. G. Marsden, *J.C.S.* 1910, **97**, 583.

[2] J. C. W. Frazer, *Amer. Chem. J.* 1903, **30**, 323; W. M. Fischer, *Z. phys. Chem.* 1918, **92**, 581.

which, although formerly regarded as possible though improbable, is now known to be impossible. The distance between two meta carbon atoms (for a regular hexagon) is 2·5 A, and that between two ortho carbon atoms is only 1·4 A, and the lengths of the covalent links are sharply determined and not capable of any serious modification. It is further to be noted that a regular alteration of colour of the salts of the nitrophenols occurs in passing from the ortho through the meta to the para series, and the salts are probably best regarded, in the present state of our knowledge, merely as being derived from the three true phenolic forms in all cases. A further reason for rejecting the view that the anion of a nitrophenol can exist either in a quinonoid or in a benzenoid form is that the two forms (IV and V) differ only in the mode of linkage of the atoms, and thus are not capable of separate existence; the true nitrophenol and the *aci*-compound (II) must give rise to a common ion.

Chelate o-*Nitrophenol Derivatives*

The three mononitrophenols show remarkable differences in physical properties. The meta and para are almost or quite colourless, while the ortho is definitely yellow. Again, while ortho, meta, and para isomers boil as a rule within 10° of one another (e.g. the three isomeric cresols), *o*-nitrophenol boils at 214° and *p*-nitrophenol at about 295°. Further examination of their physical properties shows[1] that the meta and para compounds resemble one another in the same way as meta and para compounds in general, while the ortho exhibit marked differences, being far more volatile, less soluble in water, and far more soluble (even when allowance is made for the difference in melting-point) in non-associated solvents like benzene. For example, *m*-nitrophenol is totally miscible with water at 98·7°, and para at 92·8°, while the mutual solubility of the ortho compound and water is only 10 per cent. at 200°.[2] Similar differences occur with the dinitrophenols, those which have a nitro group in the ortho position to the hydroxyl behaving like ortho nitrophenol,[3] and with other substituted phenols such as the hydroxyaldehydes and the hydroxyacetophenones.

This difference means that while the meta and para compounds have the normal behaviour of associated hydroxylic compounds, the ortho have not; the associating power of their hydroxyl group is in some way suppressed. The difference is shown in their chemical properties as well; *m*- and *p*-nitrophenol combine with aniline and *p*-toluidine, but the ortho compound does not.[4]

[1] See especially N. V. Sidgwick and R. K. Callow, *J.C.S.* 1924, **125**, 527.

[2] N. V. Sidgwick, W. J. Spurrell, and T. E. Davies, ibid. 1915, **107**, 1202.

[3] N. V. Sidgwick and W. M. Aldous, ibid. 1921, **119**, 1001; Sidgwick and T. W. J. Taylor, ibid. 1922, **121**, 1853.

[4] R. Kremann and O. Rodinis, *Monats.* 1905, **27**, 125; R. Kremann and B. Petrischek, ibid. 1917, **38**, 385; J. C. Philip, *J.C.S.* 1903, **83**, 820.

Since this behaviour is confined to the ortho series, it must be due either to ring closure or to steric hindrance; since it depends on the chemical nature of the substituent other than hydroxyl (it occurs, for example, with the hydroxyaldehydes, but not with the homologues of phenol), it cannot be due to steric hindrance, and it can only be explained by supposing that the hydroxylic hydrogen forms a hydrogen-bond[1] with the oxygen of the nitro (or aldehyde) group.
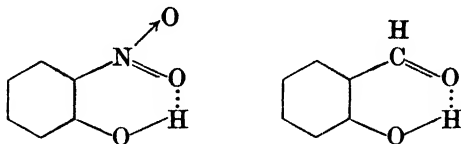
This form of chelate ring—a 6-ring with two double links—occurs in other compounds, for example in the chelate derivatives of the β-diketones, the β-ketonic acids, &c.[2]

That such combination between the phenolic hydroxyl and the nitro group is possible, is shown by the work of Auwers.[3] He finds that the introduction of a nitro group into phenol (1) in the ortho position diminishes, and (2) in the meta and para positions increases, the association of phenol, as determined by its cryoscopic behaviour in benzene; but that (3) if the nitro group is introduced into the solvent, i.e. if the molecular weights are determined in nitrobenzene, the association of ordinary phenol is found to be much less than in benzene. The assumption of combination between the hydroxyl and the NO_2 accounts for all these three effects. Phenol is associated owing to the combination of the hydroxyl groups with one another. In o-nitrophenol (1) the hydroxyl is combined with the nitro group in the same molecule and the association disappears. In m- and p-nitrophenol (2) this intramolecular combination is impossible, since a second ring cannot be formed except in the ortho position; hence the combination is between the hydroxyl of one molecule and the NO_2 of another, and the association is increased. If phenol is dissolved in nitrobenzene (3), the hydroxyl hydrogen unites to some extent with the nitro group of the solvent, instead of with the hydroxyl oxygen of a second molecule of phenol; this breaks down the association of the phenol, and the molecular weight as determined cryoscopically is more nearly normal.

In suitable circumstances both oxygen atoms of the nitro group can act as donor atoms. Thus in 2-nitroresorcinol, two six-membered chelate rings are produced, and the compound, which is red in colour, very closely resembles o-nitrophenol in its physical properties.[4] Its boiling-point

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[1] See the Introduction for the interpretation of the hydrogen-bond.

[2] See N. V. Sidgwick, *Electronic Theory of Valency*, 1926, p. 247.

[3] K. v. Auwers, *Z. phys. Chem.* 1895, **18**, 595; 1899, **30**, 300; 1903, **42**, 513; v. Auwers and K. J. P. Orton, ibid. 1897, **21**, 337.

[4] W. Baker, *J.C.S.* 1934, 1687.

(234°) is actually lower than that of resorcinol (281°), and it is completely non-associated in benzene.
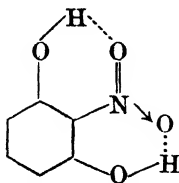
The existence of this chelate form in the free nitrophenol suggests that a similar structure may also be found among the metallic derivatives. It would be shown by a lowering of the melting-point and an increased solubility in non-dissociating solvents; it would of course be confined to those nitrophenols which have a nitro group in the ortho position to the hydroxyl. This does not seem to occur among the ordinary nitrophenol derivatives of the metals, which have the full character of salts; they have very high melting-points and are insoluble in hydrocarbons. It is, however, possible to prepare undoubted chelate o-nitro-derivatives with a metal atom in the ring. If salicylic aldehyde is added to solid sodium o-nitrophenate the colour changes to bright yellow, and a solid of the composition of $NO_2 \cdot C_6H_4ONa, 2C_6H_4(OH)CHO$ is formed.[1] This is soluble in toluene (giving a yellow solution), which shows that it is a non-ionized compound; if the toluene solution is heated the compound dissociates (less readily in presence of excess of the aldehyde), and the red sodium o-nitrophenate is deposited. This compound must have the formula
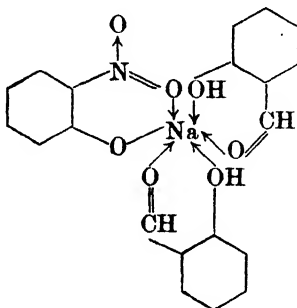
<div align="right">N. V. S.</div>

[1] N. V. Sidgwick and F. M. Brewer, *J.C.S.* 1925, **127**, 2385; F. M. Brewer, ibid. 1931, 361.

CHAPTER IX

CARBONIC ACID DERIVATIVES

THE more important nitrogen derivatives of carbonic acid, $O=C(OH)_2$, are:

1. The monamide, $O=C\begin{smallmatrix}NH_2\\OH\end{smallmatrix}$, carbamic acid; the acid does not exist in the free state but many of its derivatives are known.
2. The diamide, $O:C(NH_2)_2$, urea or carbamide.
3. The diimide, $HN:C:NH$, a few of the derivatives of which are known.
4. The amidine, $HN:C(NH_2)_2$, guanidine.

The imide of carbonic acid, $O:C:NH$, is isocyanic acid, which is more conveniently considered, in its tautomeric form $HO \cdot C\equiv N$, as a cyanogen compound. Many of the above derivatives give rise to corresponding thio compounds, in which oxygen is replaced by sulphur.

Carbamic Acid

The free acid is not known; reactions by which it might be formed always give its decomposition products, ammonia and carbon dioxide. Its ammonium salt, however, is readily accessible, because it is produced by the direct combination of ammonia and carbon dioxide in the gas phase or, better, in a cooled inert solvent such as absolute alcohol or petroleum ether. It is precipitated as a crystalline powder which is somewhat volatile and is not stable in contact with moist air. From this other salts can be obtained by double decomposition, if precautions are taken to avoid the hydrolysis of the carbamate ion. The sodium salt can also be obtained by the hydrolysis of sodium cyanamide in aqueous alcohol:

$$NaNH \cdot CN + 2H_2O \longrightarrow O=C\begin{smallmatrix}NH_2\\ONa\end{smallmatrix} + NH_3.$$
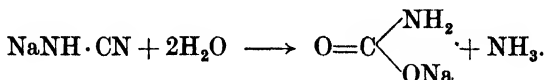
The carbamates can be readily distinguished from the carbonates because calcium carbamate is soluble in water, and hence addition of a soluble calcium salt to a solution of a carbamate gives no precipitate: on standing, or more rapidly on heating, calcium carbonate appears through the hydrolysis of carbamate to carbonate:

$$NH_4O_2C \cdot NH_2 + H_2O \longrightarrow (NH_4)_2CO_3.$$
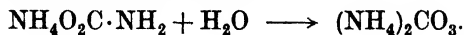
The hydrolysis of ammonium carbamate has been studied by C. Faurholt,[1] who has shown that the behaviour is by no means simple. In very weakly acid solution the decomposition of carbamate is complete in less than one second, and it can be demonstrated that the products of decomposition

[1] *Z. anorg. Chem.* 1921, **120**, 85.

are initially ammonia and carbon dioxide and not the ammonium and carbonate ions. This is possible because carbon dioxide and carbonic acid differ, in that the former in the presence of excess of ammonia reforms ammonium carbamate while the latter gives ammonium carbonate. If a solution of ammonium carbamate is made weakly acid, after one second no carbonate can be detected, but addition of ammonia reconverts the whole to carbamate. On the other hand, if a solution of sodium carbonate is acidified, carbonic acid is liberated, and immediate addition of ammonia gives no carbamate. On standing the equilibrium $CO_2 + H_2O \rightleftharpoons H_2CO_3$ is set up, the process requiring some seconds, so that after an interval both of the above solutions behave similarly when excess of ammonia is added. It thus appears that the actual mechanism of the apparent hydrolysis of ammonium carbamate in weakly acid solution is best represented by the equations

$$NH_2 \cdot CO_2^- + NH_4^+ \;\rightleftharpoons\; 2NH_3 + CO_2 \qquad NH_3 + H^+ \;\rightleftharpoons\; NH_4^+$$
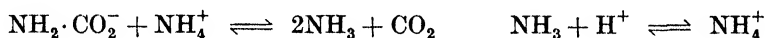
both processes being reversible and proceeding very rapidly. In solution in pure water or in the presence of ammonia with or without ammonium salts, the behaviour of ammonium carbamate is different; a true equilibrium between carbamate and carbonate is set up, in which the concentration of carbamate is much increased by increasing the concentration of ammonia. The equilibrium is $NH_2 \cdot CO_2^- + H_2O \;\rightleftharpoons\; HCO_3^- + NH_3$, or $NH_2 \cdot CO_2^- + H_2O \;\rightleftharpoons\; CO_3^{--} + NH_4^+$, but the mechanism whereby it is set up again seems to be regulated by the speed at which carbon dioxide is hydrated to carbonic acid. The primary process again can be shown to be $NH_2 \cdot CO_2^- + NH_4^+ \;\rightleftharpoons\; 2NH_3 + CO_2$, an equilibrium which is established very rapidly, after which the carbon dioxide-carbonic acid equilibrium is established more slowly. Finally, in solutions containing caustic alkalis ammonium carbamate is much more stable, and though decomposition is eventually complete, and there is no equilibrium, several days are needed at room temperature for complete hydrolysis.

Ammonium carbamate on heating is partially converted into water and urea, and it is manufactured for this purpose in one of the industrial methods of obtaining urea.

The acid chloride of carbamic acid, $H_2N \cdot COCl$, can be obtained by passing dry hydrogen chloride over potassium cyanate or cyanuric acid or cyamelide: it is a somewhat unstable liquid boiling at 61–62° with decomposition into hydrogen chloride and cyanic acid; the latter partly polymerizes, as usual, into cyamelide and cyanuric acid. The same change takes place slowly at room temperature. It behaves as a normal acid chloride in the Friedel-Crafts reaction, giving with aromatic hydrocarbons in the presence of aluminium chloride the amide of the aromatic carboxylic acid. Water decomposes it immediately to ammonium chloride and carbon dioxide.

The esters of carbamic acid are usually described as urethanes, the word urethane itself commonly referring to the ethyl ester $H_2N \cdot CO_2Et$.

Urethane is used to some extent as a hypnotic for children and as an anaesthetic for animals: some of its derivatives find similar uses. The urethanes are crystalline solids, usually soluble in water, alcohol, and benzene, while the N-alkyl urethanes are liquids. They are all stable compounds and boil without decomposition. They can be obtained in the following ways:

(a) By the action of ammonia or an amine on esters of carbonic acid or chloroformic acid:

$$Cl \cdot CO_2Et + NH_3 \longrightarrow H_2N \cdot CO_2Et.$$

(b) By the interaction of an alcohol and carbamyl chloride.

(c) From an alcohol and cyanic acid:

$$HN:C:O + EtOH \longrightarrow H_2N \cdot CO_2Et.$$
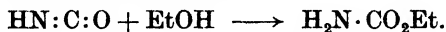
If an ester of isocyanic acid is used, a substituted urethane is obtained; thus phenyl isocyanate and ethyl alcohol give phenyl urethane. This reaction has sometimes been used to detect the presence of a hydroxyl group, and to identify an alcohol, since the phenyl urethanes have convenient melting-points. It can also be applied to distinguish between hydroxyl and imino groups, since with the latter ureas and not urethanes are formed.

(d) From urea, either by heating with an alcohol,

$$(H_2N)_2CO + ROH \longrightarrow H_2NCO_2R + NH_3,$$
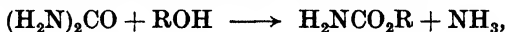
the reversal of the ordinary reaction of amide formation from an ester and ammonia, or more conveniently by dissolving urea nitrate in the alcohol and adding slowly one equivalent of sodium nitrite. The latter method, which is very convenient for the preparation of urethane itself and gives a yield of 80 per cent. of the theoretical amount,[1] would appear to involve the esterification of carbamic acid formed by the action of nitrous acid on urea.

The simple urethanes behave in many ways like amides. They react with sodium in dry ether with evolution of hydrogen to give sodium derivatives which are decomposed by water and have been used for the synthesis of other derivatives which are mentioned below. They are hydrolysed by aqueous acids and alkalis to an alcohol, ammonia, and carbon dioxide:

$$H_2N \cdot CO_2R \longrightarrow NH_3 + CO_2 + ROH.$$

With alcoholic potash, however, they are decomposed to potassium cyanate:

$$H_2N \cdot CO_2Et \longrightarrow KOCN + EtOH.$$
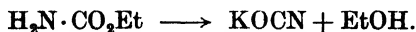
N-chloro-urethane, a colourless liquid only slightly soluble in water, can be readily obtained by the action of chlorine on an aqueous solution of urethane. It shows the typical reactions of N-chloro compounds, liberating iodine from potassium iodide and being readily reduced to

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[1] L. Guerci, *Zent.* 1922, i. 1104.

T

urethane.[1] N-Nitro-urethane obtained by the action of ethyl nitrate on urethane in solution in concentrated sulphuric acid at a low temperature[2] is not a very stable substance and resembles nitro-urea in being a strong acid: it reacts with aniline to give nitrous oxide and phenylurethane, $\phi NH \cdot CO_2Et$.

The N-alkyl urethanes contain a secondary amino group and hence can react with nitrous acid to give N-nitroso compounds. The simplest of these, nitrosomethylurethane, $ON \cdot NMe \cdot CO_2Et$, was formerly of importance, in that its hydrolysis by methyl alcoholic potash was the most convenient method of obtaining the valuable reagent diazomethane. The primary product of the hydrolysis, nitrosomethylamine or its alkali salt, decomposes to diazomethane and water:

$$ON \cdot NMe \cdot CO_2Et \xrightarrow{H_2O} CO_2 + EtOH + ON \cdot NHCH_3 \longrightarrow CH_2N_2 + H_2O.$$
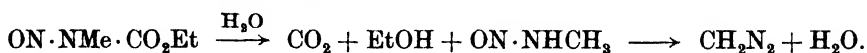
This method is, however, less convenient and more expensive than the preparation of diazomethane from nitrosomethylurea (see p. 289).

The sulphur analogue of carbamic acid is only known in the form of its salts and esters, certain of which are used as agents for killing the spores of injurious rusts and moulds in soil. The esters are derived from each of the two possible structures of the acid, $H_2N \cdot CS \cdot OH$ and $H_2N \cdot CO \cdot SH$. The O-esters, $H_2N \cdot CS \cdot OR$, can be obtained by the action of alcoholic ammonia on the O,S-diesters of dithiocarbonic acid, an example of the normal formation of an amide:

$$EtS \cdot CS \cdot OEt + NH_3 \longrightarrow H_2N \cdot CS \cdot OEt.$$
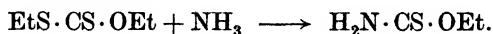
Their structure is shown by their decomposition by alkalis to alcohol and a salt of thiocyanic acid. The S-esters are best obtained by the interaction of an alcohol with thiocyanic acid in presence of hydrogen chloride:

$$HSCN + EtOH \longrightarrow EtS \cdot CO \cdot NH_2.$$
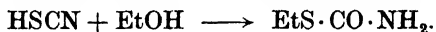
On hydrolysis they yield mercaptans, a reaction which proves their structure.

The acid chloride of thiocarbamic acid, $H_2N \cdot CS \cdot Cl$, can be prepared by the action of hydrogen chloride on thiocyanic acid in dry ether.[3] It is a white powder which decomposes without melting: it reacts with alcohols and phenols to give as principal product the O-esters of the acid.

Dithiocarbamic acid, $H_2N \cdot CS \cdot SH$, can be obtained as an unstable solid by the action of mineral acids on its ammonium salt, which is formed together with other products by the interaction of alcoholic ammonia and carbon disulphide. It can give rise to only one series of esters, which are most readily obtained by the action of alkyl iodides on the ammonium

[1] W. Traube and H. Gockel, *Ber.* 1923, **56**, 384.

[2] A. Lachman and J. Thiele, ibid. 1894, **27**, 1520.

[3] M. Battegay and E. Hégazi, *C.r.* 1933, **196**, 1030; *Helv. Chim. Acta*, 1933, **16**, 999.

salt. If an α-chloro-ketone replaces the alkyl iodide, the product easily undergoes ring closure to a thiol derivative of a thiazole.[1]

$$
\underset{S=C\diagdown_S\diagup CH_2}{\overset{NH_2\quad CO\cdot CH_3}{|}} \longrightarrow \underset{HS\cdot C\diagdown_S\diagup CH}{\overset{N\!-\!-\!-\!C\cdot CH_3}{||}}
$$
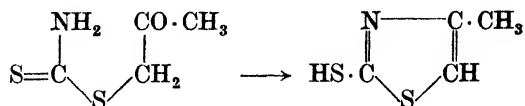
The salts and esters of the N-substituted dithiocarbamic acids, e.g. $EtNH\cdot CS\cdot SNH_4$, can be obtained in a similar fashion using amines in the place of ammonia. Thus carbon disulphide reacts readily with methyl-amine to give the methylammonium salt of N-methyldithiocarbamic acid. With aromatic amines carbon disulphide can react to give thio-carbanilides (see p. 292), but in the presence of aqueous ammonia[2] or of metallic hydroxides,[3] they behave like aliphatic amines and the ammonium or metallic salt of phenyldithiocarbamic acid (dithiocarbanilic acid) is formed.

$$
S=C=S + 2H_2NR \longrightarrow S=C\diagup^{S[NH_3R]}_{\diagdown NHR}
$$
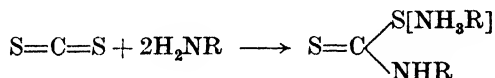
The free acid is unknown and the salts are not at all stable: if warmed with solutions of salts of lead, zinc, or iron, they decompose to the metallic sulphide and phenylisothiocyanate (phenyl mustard oil), and thus serve as convenient intermediates for the preparation of the latter:[4]

$$
S=C\diagup^{NH\phi}_{\diagdown S[NH_4]} \longrightarrow S:C:N\phi + H_2S + NH_3.
$$
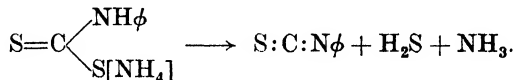
Urea

Urea, which is also called carbamide, is the amide of carbonic acid, $CO(NH_2)_2$, and is one of the most important of the simple nitrogenous compounds; in addition to its historical interest—its preparation from ammonium cyanate by Wöhler[5] in 1828 having gone far to break down the barriers that had been erected between organic and inorganic chemistry—it is of importance from the points of view of physiology and industrial chemistry, and the study of its reactions and properties has raised several very interesting questions in theoretical chemistry.

Urea was discovered in urine by Rouelle in 1773, and its composition was first established by Prout[6] in 1818. It is the most important form in which nitrogen is excreted by mammals; in the case of man about 80 per cent. of the total excreted nitrogen is in the form of urea, an adult man excreting about 1 ounce in 24 hours. This urea is synthesized by the body from ammonia and carbon dioxide, and the liver is the only organ in

[1] T. G. Levi, *Gazz.* 1931, **61**, 719.   [2] S. M. Losanitch, *Ber.* 1891, **24**, 3022.
[3] R. Krulla, ibid. 1913, **46**, 2669.
[4] *Organic Syntheses*, Collective vol. 1, 1932, p. 437.   [5] *Pogg. Ann.* 1828, **12**, 253.
[6] For history see F. D. Chattaway, *Chem. News*, 1909, **99**, 121.

which the synthesis takes place. H. A. Krebs and K. Henseleit[1] have carried out an extensive investigation on the mechanism of this synthesis and have sho /n that the primary reaction is that of ammonia and carbon dioxide with the amino-acid ornithine present in the liver to give the ureido-acid citrulline: this reacts further with ammonia and the guanidino-acid, arginine, is formed. The final step is hydrolysis of arginine to urea

$$HO_2C \cdot CHNH_2 \cdot (CH_2)_3NH_2 \longrightarrow HO_2C \cdot CHNH_2(CH_2)_3NH \cdot CO \cdot NH_2 \longrightarrow$$

ornithine   citrulline

$$HO_2C \cdot CHNH_2 \cdot (CH_2)_3NH \cdot C(:NH) \cdot NH_2 \longrightarrow ornithine + urea$$

arginine
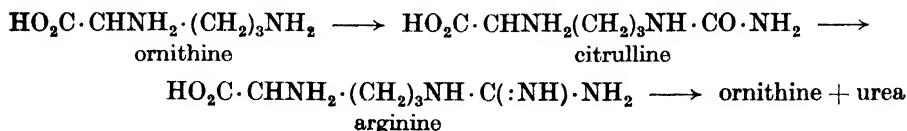
and ornithine. All these reactions, of course, take place under the influence of the enzymes present in the liver, and of these arginase, the hydrolytic enzyme active in the last stage, has been known for many years. The livers of both reptiles and amphibia are capable of the same urea synthesis,[2] but with reptiles the principal form in which nitrogen is excreted is not urea, but its derivative uric acid.

Urea occurs very widely in animal tissues and fluids and also in the plant kingdom.[3] In the latter it appears to be of special importance in the fungi; these are able to synthesize urea from ammonia or its salts, and use it as an intermediate reserve product for storing nitrogen; when favourable conditions arise, the urea is broken down with reformation of ammonia, which is used for the synthesis of proteins. In this way urea plays in the fungi the part which among the higher plants is played by the amides asparagine, $HO_2C \cdot CH(NH_2) \cdot CH_2 \cdot CONH_2$, and glutamine,[4]

$$HO_2C \cdot CH(NH_2) \cdot (CH_2)_2 \cdot CONH_2.$$
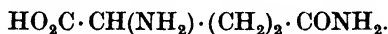
Of the methods for obtaining urea in the laboratory, the greatest interest attaches to Wöhler's method, the isomeric change of ammonium cyanate into urea. If an aqueous solution of ammonium cyanate is evaporated to dryness on the water bath, the residue consists almost entirely of urea; solid ammonium cyanate, which is stable at room temperature for a day or two, is almost wholly transformed into urea by heating to 60° for five hours and in the region of 80° melts and immediately resolidifies as urea:[5]

$$NH_4 \cdot NCO \longrightarrow CO(NH_2)_2.$$
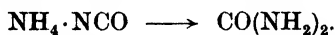
In aqueous solution the change is reversible;[6] at 100° in aqueous solution equilibrium is reached when 95 per cent. of the ammonium cyanate has changed into urea, and the latter, when its solution is kept at 100°, is converted to the extent of 5 per cent. into ammonium cyanate.

The rate of the change has been measured in various solvents and with

[1] Z. physiol. Chem. 1932, 210, 33.

[2] H. Manderscheid, Biochem. Z. 1933, 263, 245.

[3] See K. Tauböck and A. Winterstein: G. Klein's Handbuch der Pflanzanalyse, Berlin, 1933, vol. iv, Part 3, p. 197.

[4] N. N. Ivanoff, Biochem. Z. 1924, 154, 376.

[5] J. Walker and J. K. Wood, J.C.S. 1900, 77, 30.

[6] J. Walker and F. J. Hambly, ibid. 1895, 67, 748.

addition of other substances; it has been found to take place much more rapidly in alcohol than in water and to be proportional to the product of the concentrations of the ammonium and cyanate ions. This result is of historical importance because it was discovered at a time when the existence of ions in solution was a matter of controversy, and it provided the supporters of their existence with a powerful argument. Such a result does not, however, throw any direct light on the mechanism of reaction; the product of the concentrations of the ammonium and cyanate ions must be proportional to the concentration of any undissociated form of ammonium cyanate, and this again must be proportional to the concentrations of any other substances into which ammonium cyanate can dissociate. Hence the fact that the rate of the reaction varies with the concentrations of the ions is not conclusive; the reaction may involve the ions, or the undissociated molecule, or any other dissociation products of the molecule. Consideration, however, of analogous reactions, such as the formation of N-alkyl ureas by the action of ammonia or primary or secondary amines on isocyanic esters, a reaction mentioned below, indicates that the primary step is the dissociation of the ammonium cyanate into ammonia and cyanic acid; the latter contains the carbonyl group which possesses the well-known tendency to add on ammonia or its analogues, as in aldehyde-ammonia formation, and thus the two products of dissociation react by addition:[1]

$$NH_4 \cdot NCO \longrightarrow NH_3 + HN{:}C{:}O \longrightarrow HN{=}C{\Big\langle}{}^{OH}_{NH_2} \longrightarrow CO(NH_2)_2.$$
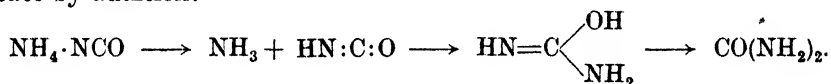
This view is an adequate explanation of the well-known fact that during the transformation some ammonia is always lost and some cyanuric acid and cyamelide (both polymerized forms of cyanic acid) are formed.

Since urea is the amide of carbonic acid, it should be formed by the action of ammonia on the acid chloride or the esters of carbonic acid. It can in fact be obtained from carbonyl chloride and ammonia, but the yield is small because the intermediate product, carbamyl chloride, $Cl \cdot CO \cdot NH_2$, loses hydrogen chloride very easily to give cyanic acid which, as usual, polymerizes to cyanuric acid and cyamelide. John Davy in 1812 was the first to allow carbonyl chloride and ammonia to interact, and he must have obtained some urea, but he failed to recognize it as such. Urea is also formed when ammonia acts upon ethyl carbonate, but in bad yield because of the stability of the intermediate urethane, $EtO \cdot CO \cdot NH_2$: the yield is excellent, however, if phenyl carbonate is used.

Urea is nowadays manufactured on a large scale in chemical industry. A century ago the artificial production of a small quantity by Wöhler was a noteworthy achievement: to-day the routine output of a fertilizer factory is of the order of 100 tons a day. There are two principal methods. The first is the partial hydrolysis of cyanamide, $N{:}C \cdot NH_2 \to CO(NH_2)_2$, the cyanamide coming from the calcium cyanamide obtained by the

[1] F. D. Chattaway, J.C.S. 1912, **101**, 170.

electric furnace method from calcium carbide; the hydrolysis to urea takes place in weakly acid solution and sometimes metallic oxides are added as catalysts.[1] The second process is the direct synthesis from ammonia and carbon dioxide. G. N. Lewis and G. H. Burrows[2] carried out a thermodynamic investigation of the free energy of formation of urea by the reaction $CO_2 + 2NH_3 \rightleftharpoons CO(NH_2)_2 + H_2O$, and from their results it could be seen that under suitable conditions good yields of urea could be obtained; the interesting experiments of C. Matignon and M. Fréjacques[3] also deserve mention. In practice ammonium carbamate obtained from carbon dioxide and ammonia is heated under 33–35 atmospheres to 130–150° and yields of 30–45 per cent. of urea in the equilibrium $NH_2 \cdot CO_2NH_4 \rightleftharpoons H_2O + CO(NH_2)_2$ are obtained. A. Klemenc has investigated the analogous preparation from ammonia and carbon oxysulphide[4] and has shown that this process should be superior to the other, the product being free from carbamate and carbonate and the yield twice as large.

The practical uses for urea have increased largely in recent years, in consequence of its cheapness and accessibility from Haber-process ammonia by the above method. It is becoming more and more important as a fertilizer in agriculture, since it contains nearly 47 per cent. of readily available nitrogen (two or three times as much as compounds such as $(NH_4)_2SO_4$ or $NaNO_3$), and it is remarkably free from secondary effects on the soil. It is the starting-point for the preparation of many drugs, such as veronal (diethyl malonyl urea), and for the manufacture of the urea-formaldehyde resins used for unbreakable tableware.

Urea forms long colourless prisms which melt at 132·7°. The crystal structure has been investigated in the greatest detail[5] and is one of the most fully known of all organic compounds: its bearing on the chemistry of urea is mentioned below. Urea is a weak monacid base and its solution is neutral; its salts, however, are stable and are all soluble in water, the oxalate and the nitrate having the smallest solubility: the latter is practically insoluble in strong nitric acid and is thus sometimes used for the isolation of urea.

As an amide, urea is hydrolysed by both acids and alkalis to ammonia and carbon dioxide: the rate of hydrolysis has been measured,[6] and the results show that the behaviour differs in several respects from that of an ordinary amide such as acetamide. In all cases the reaction is initially of the first order, because the concentration of the hydrolysing agent (the H_3O^+ ion in acid solution or the OH^- ion in alkaline) remains almost

[1] See, e.g., D.R.-P. 487307; *Fried.* 1931, **16**, 272.

[2] *J. Amer. C. S.* 1912, **34**, 1515.   [3] *Ann. Chim.* 1922, [ix], **17**, 257.

[4] *Z. anorg. Chem.* 1930, **191**, 246.

[5] S. B. Hendricks, *J. Amer. C. S.* 1928, **50**, 2455; R. W. G. Wyckoff, *Z. Krist.* 1931, **81**, 102; 1933, **85**, 132.

[6] C. E. Fawsitt, *Z. phys. Chem.* 1902, **41**, 603; G. J. Burrows and C. E. Fawsitt, *J.C.S.* 1914, **105**, 609.

constant, especially if it is in large excess. With acetamide the hydrolysis by alkalis is much more rapid than by acids, while with urea the reverse is true, and in addition the rate of hydrolysis by acids is, within wide limits, independent of the hydrogen-ion concentration. Fawsitt explains this abnormal behaviour as being due to the equilibrium between urea and ammonium cyanate in aqueous solution. Cyanates are very readily hydrolysed by acids and much less easily by alkalis; hence the hydrolysis of urea by acids is really the hydrolysis of the cyanate in equilibrium with it, and this proceeds much more rapidly than that of the urea itself. The velocity of hydrolysis will thus be determined by the rate of the isomeric change of urea into ammonium cyanate and be independent of the concentration of the hydrolysing agent, the hydrogen ion.

The hydrolysis of urea also takes place under the influence of certain enzymes, of which urease is the most important. This enzyme occurs in bacteria and in plants: the most abundant sources are the soya bean of China and Japan and the jack bean (*Canavalia ensiformis*) of the United States. It seems to be specific in its action on urea and incapable of bringing about the hydrolysis of any other substance, with the exception of certain N-alkyl ureas: for this reason it is of great importance for the quantitative estimation of urea, which is discussed below. The enzyme has been obtained in a crystalline state[1] and is a protein.

Like other amides urea reacts with nitrous acid in the presence of mineral acids to give nitrogen: the reaction was formerly used for the quantitative estimation of urea, but by-products are always formed, notably nitric oxide,[2] and the method is only approximate. The action of hypobromites or hypochlorites on urea (the Hofmann reaction) appears to differ from their action on other amides, since the urea is oxidized to nitrogen: this reaction has also been used for estimating urea, but again the results are very inaccurate.[3] The difference is more apparent than real, since the expected product of the Hofmann reaction with urea would be hydrazine, $NH_2 \cdot NH_2$, and this is in fact formed and quickly oxidized to nitrogen by the hypobromite. The intermediate formation of hydrazine was shown by P. Schestakov,[4] who found that if benzaldehyde is added to the reaction mixture, good yields of benzalazine, $\phi CH:N \cdot N:CH\phi$, the condensation product of hydrazine and benzaldehyde, can be obtained.

Urea on heating decomposes a little above its melting-point and dissociates into ammonia and cyanic acid. If not heated too strongly, some of the cyanic acid combines with unchanged urea to give biuret:

$$H_2N \cdot CO \cdot NH_2 + HNCO \longrightarrow H_2N \cdot CO \cdot NH \cdot CO \cdot NH_2.$$
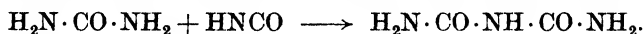
Biuret gives a reddish violet colour when treated with copper sulphate and alkali and this so-called biuret reaction is sometimes used as a test

[1] J. B. Sumner, *J. biol. Chem.* 1926, **69**, 435; 1928, **76**, 149; see also H. Tauber, ibid. 1930, **87**, 625; F. Kubowitz and E. Haas, *Biochem. Z.* 1933, **257**, 337.

[2] E. A. Werner, *J.C.S.* 1917, **111**, 844.

[3] L. Ambard, *Bull. Soc. Chim. biol.* 1920, **2**, 205.

[4] *J. Russ. Phys. Chem. Soc.* 1905, **37**, 1; *Zent.* 1905, ii. 1703.

for urea. If heated strongly, urea loses its ammonia and the cyanic acid polymerizes, as usual, to a mixture of cyanuric acid and cyamelide: this is a convenient method for obtaining cyanuric acid. If the heating is continued, the cyanuric acid volatilizes as cyanic acid.

There are two important methods for the quantitative estimation of urea. The first, already referred to, takes advantage of the specific hydrolytic action of urease on urea; the enzyme is most active at a hydrogen-ion concentration of $10^{-7.2}$, so that suitable buffers are used, and the optimum temperature is 45°. After hydrolysis either the carbon dioxide or the ammonia can be estimated.[1] The second method is that of R. Fosse;[2] in the presence of a little acetic acid urea combines with xanthydrol,
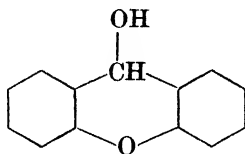
to give the very stable dixanthydryl-urea, of constitution
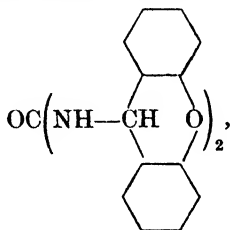
which is completely insoluble in acetic acid, water, and cold alcohol. The only allied substances which will react similarly with xanthydrol are certain easily decomposed ureides. The estimation is by weighing the precipitate, or a volumetric modification devised by F. W. Allen and J. M. Luck.[3]

Although the constitution of urea as being the amide of carbonic acid has been recognized since the work of J. B. A. Dumas (1830), all the questions of its fine structure are by no means settled, and in particular it is not at the moment certain whether the formula (I) best expresses its behaviour under all circumstances.
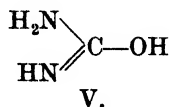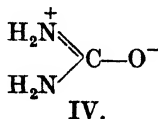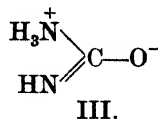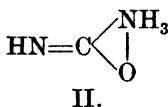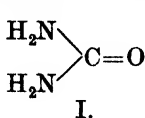
[1] E. K. Marshall, *J. biol. Chem.* 1913, **15**, 487, 495.

[2] *C.r.* 1914, **158**, 1076, 1588; **159**, 250.

[3] *J. biol. Chem.* 1929, **82**, 693 (for details see K. Tauböck and A. Winterstein, G. Klein's *Handbuch der Pflanzanalyse*, Berlin, 1933, vol. iv, part 3, p. 209).

Many of the points that arise in this connexion are identical with those that arise in the case of thio-urea, and it will be convenient to discuss the constitution of the two substances together. In 1913 Emil A. Werner[1] put forward the view that a better formula is (II), and this view he maintained in a series of papers.[2] His formula seems to have been accepted widely, especially among biological chemists, although it is difficult to understand most of the reasons which led to its proposal. Discussion of it, however, raises several points of interest and certainly indicates that there may be more behind the structure than appears from formula (I).

As it stands, Werner's formula (II) is extremely improbable, a fact pointed out by I. Langmuir.[3] It implies a nitrogen atom with five covalencies, a state in which nitrogen has not yet been found, and which from almost any theory of atomic structure is very unlikely. There is nothing so exceptional in the chemistry of urea as would lead us to postulate nitrogen in such a state of combination. The only meaning that can be attributed to Werner's formula is shown in formula (III); this formula, which is identical with (II) except that the atoms are in a more likely state, implies that the urea molecule is an internal salt, the oxygen atom bearing a negative, and a nitrogen atom a positive charge: the formula is analogous to the so-called zwitterion formulae of the aliphatic amino-acids and the betaines. If, however, such a zwitterion state of the urea molecule is possible, it is almost certainly that represented in formula (IV) and not in (III): in other words, if one cares to think of the tautomeric form of urea (V) which contains a hydroxyl group and basic nitrogen atoms, then internal salt formation is much more likely to take place by the migration of the hydrogen ion of the hydroxyl group to the imino nitrogen atom than to the amino nitrogen atom. This is known from the admirable work of H. Lecher and his collaborators on thio-urea and guanidine.[4] These compounds present an exactly analogous problem. With thio-urea, is the zwitterion form (VI) or (VII)? And with guanidine, is the monacid salt (VIII) or (IX)?

$$\bar{S}\!-\!C\!\!\begin{array}{c}\nearrow NH_2 \\ \searrow NH_2^+ \end{array} \qquad \bar{S}\!-\!C\!\!\begin{array}{c}\nearrow NH_3^+ \\ \searrow NH \end{array} \qquad H_2N\!-\!C\!\!\begin{array}{c}\nearrow NH_2 \\ \searrow NH_2^+ \end{array} \qquad H_2N\!-\!C\!\!\begin{array}{c}\nearrow NH_3^+ \\ \searrow NH \end{array}$$

$$\text{VI.} \qquad\qquad \text{VII.} \qquad\qquad \text{VIII.} \qquad\qquad \text{IX.}$$
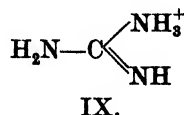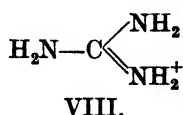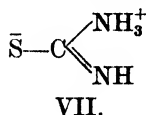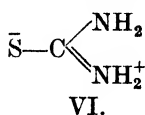
Lecher has studied the behaviour of the alkyl substituted compounds, and one example of his arguments is as follows: the two isomeric tetra-methyl compounds (X) and (XI) are known, one derived from thio-urea and the other from the tautomeric isothio-urea: they both react with methyl iodide to give one and the same product which must be (XII),

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[1] *J.C.S.* 1913, **103**, 1010.

[2] For summary see E. A. Werner, *The Chemistry of Urea*, Longmans, Green & Co. 1923.

[3] *J. Amer. C. S.* 1920, **42**, 284.

[4] *Annalen*, 1924, **438**, 169; 1925, **445**, 35, 79; 1924, **438**, 154; 1925, **445**, 61; 1927, **455**, 139.

since it is the only pentamethyl compound which can be derived from either compound.

$$S=C{\Large<}{NMe_2 \atop NMe_2} \qquad MeS-C{\Large<}{NMe_2 \atop NMe} \qquad MeS-C{\Large<}{NMe_2 \atop NMe_2^+} \quad [I]$$

$$\text{X.} \qquad\qquad\qquad \text{XI.} \qquad\qquad\qquad \text{XII.}$$
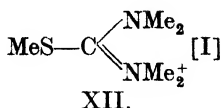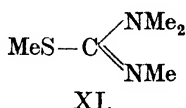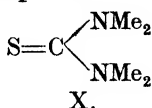
This result implies that when in (XI) one nitrogen atom becomes quaternary, it is the imino and not the amino atom. By several similar examples Lecher establishes his point and we can carry over the result to urea and reject (III) in favour of (IV). This formula and the simple formula (I) are identical in the attachment of atom to atom and differ only in electronic arrangement, (IV) being a zwitterion; there is an apparent difference in that the nitrogen atoms are in an identical state of combination in (I) and appear not to be so in (IV).

$$-C{\Large<}{NH_2 \atop NH_2^+} \qquad -C{\Large<}{O^- \atop O} \qquad -N{\Large<}{O \atop O}$$

$$\text{XIII.} \qquad\qquad \text{XIV.} \qquad\qquad \text{XV.}$$
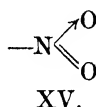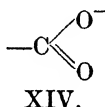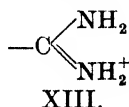
If this difference were real, then formula (IV) could be rejected at once, at least for urea and thio-urea in the solid state, because crystal structure evidence shows that in that state the two nitrogen atoms are identical. This apparent difference does not, however, exist. The group (XIII), is the analogue of the carboxylate ion (XIV); there is no doubt about the validity of the formula of this ion, but at the same time we have indisputable evidence from the analysis of the crystal structure of basic beryllium acetate that the two oxygen atoms are indistinguishable.[1] The equivalence of the two nitrogen atoms in (XIII) and of the oxygen atoms in (XIV) and (XV) is a consequence of the phenomenon of resonance which is discussed in the Introduction; the actual state of these two ions is that of a hybrid between two states, of which one is shown in (XIII), (XIV), and (XV) and the other contains the double bond between the carbon and the second nitrogen or oxygen atom. The symmetry of groups such as (XIII) was recognized before resonance was established from the basis of wave-mechanics.[2]

Now there are certain facts about urea and thio-urea which suggest that under certain circumstances the zwitterion structure (IV) is assumed. Of these the most important are the values of the dielectric constants of their aqueous solutions. R. Fürth[3] and O. Blüh[4] were the first to observe that addition of urea to water brought about a marked increase in the dielectric constant of the liquid, while addition of other organic substances such as cane sugar lowered the dielectric constant. The observations have been much extended by G. Devoto[5] who has shown that all simple

[1] G. T. Morgan and W. T. Astbury, *Proc. Roy. Soc.* 1926, **112**, A, 441; L. Pauling and J. Sherman, *Proc. Nat. Acad. Sci.* 1934, **20**, 240.

[2] e.g. H. Lecher, *Annalen*, 1925, **445**, 47.

[3] *Ann. Physik*, 1923, [4], **70**, 1.   [4] *Z. phys. Chem.* 1923, **106**, 341.

[5] *Gazz.* 1930, **60**, 520; 1933, **63**, 50, 119; *Ber.* 1931, **64**, 1329.

nitrogenous compounds such as amides lower the dielectric constant, but that urea, thio-urea, and all the aliphatic amino-acids increase it. There is still difficulty in the quantitative interpretation of such measurements,[1] but there is no doubt that the effect arises in the case of the amino-acids from their undisputed zwitterion structure. This is acknowledged by every one, so that it is difficult to avoid the conclusion that in aqueous solution urea and thio-urea are also zwitterions, a conclusion drawn by Devoto, though he adopts the erroneous formula (III). The properties of the two substances in the solid state also suggest such a structure: both urea and thio-urea have melting-points which are higher than might be expected and thus resemble the amino-acids, where we know the high melting-point arises from the internal salt structure. The arrangement of the molecules in the crystal lattice revealed by X-ray analysis[2] is with the oxygen atom of one molecule next to the amino end of another, and is described by J. D. Bernal and W. A. Wooster[3] as a 'typical polar molecular structure', but, more importantly, the measured distance between the carbon and nitrogen atoms in one molecule is too short to be normal for the true single bonds of formula (I); it is $1 \cdot 33$ A, the normal single bond distance being $1 \cdot 48$ A and for the double bond ($>C=N$—) $1 \cdot 28$ A. The fact that the observed value falls between the normal lengths for the single and double bond, and is closer to the latter, affords strong support for the view that in the solid state urea must be represented by formula (IV) and not by formula (I). Such a shortening of the normal distance between atoms is a general phenomenon in resonance-hybrids, and formula (IV) implies resonance between the nitrogen atoms.

The absorption spectra in the ultra-violet (2,300–4,300 A) of aqueous and alcoholic solutions of thio-urea and certain of its alkyl derivatives have been measured by H. Rivier and J. Borel.[4] They found that thio-urea, trimethylthio-urea, and S,N,N,N'-tetramethylthio-urea (XVI) have practically identical absorption spectra, whereas the symmetrical tetra-substituted thio-ureas (XVII) show a stronger absorption of quite different type.

$$\text{MeS—C} \begin{cases} \diagup \text{NMe}_2 \\ \diagdown \text{NMe} \end{cases} \qquad \text{S}=\text{C} \begin{cases} \diagup \text{NR}_2 \\ \diagdown \text{NR}_2 \end{cases}$$

XVI.   XVII.
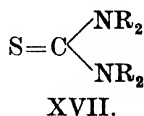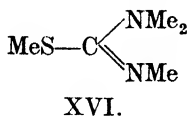
This stronger absorption can only be ascribed to the doubly linked carbon and sulphur atoms, and its absence in thio-urea gives additional evidence in favour of the zwitterion formula for that compound. The results also are in agreement with the view discussed below that *symm*-tetramethylthio-urea does not have this type of structure.

On the chemical side there are several facts that give support: one

[1] See W. Kuhn and H. Martin, ibid. 1934, **67**, 1526.

[2] S. B. Hendricks, *J. Amer. C. S.* 1928, **50**, 2455; R. W. G. Wyckoff, *Z. Krist.* 1932, **81**, 102; Wyckoff and R. B. Corey, ibid. 1934, **89**, 462.

[3] *Ann. Report C. S.* 1929, 303.   [4] *Helv. Chim. Acta*, 1928, **11**, 1219.

characteristic reaction of the zwitterion amino-acids is that they react with methyl iodide or methyl sulphate to give the methyl ester of the acid, a reaction which does not take place with an ordinary carboxylic acid.

$$\overset{+}{N}H_3 \cdot CH_2 \cdot CO_2^- \xrightarrow{MeI} \overset{+}{N}H_3 \cdot CH_2 \cdot CO_2Me \; [I]^-$$
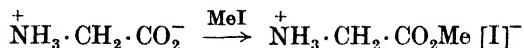
The same reaction occurs with urea;[1] on heating urea with methyl sulphate, O-methylurea is formed: the methylation on the oxygen atom is strongly suggestive of a zwitterion structure.

$$\begin{matrix} H_2N \\ {}_{\overset{+}{H_2N}} \end{matrix}\!\!>\!\!C\text{—}O^- \xrightarrow{MeX} \begin{matrix} H_2N \\ {}_{\overset{+}{H_2N}} \end{matrix}\!\!>\!\!C\text{—}OMe \; [X]^-.$$
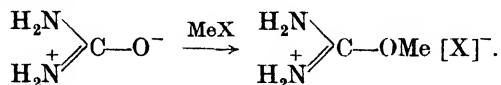
The same is true of thio-urea, which always alkylates and acylates on the sulphur atom and not on a nitrogen atom.[2] Lastly, the fact that urea is a monacid base is readily explained by formula (IV); the molecule can take up a proton on the negatively charged oxygen atom to give the cation

$$\begin{matrix} H_2N \\ {}_{\overset{+}{H_2N}} \end{matrix}\!\!>\!\!C\text{—}OH,$$

and this will have a low energy content because of the resonance between the nitrogen atoms, and hence will be stable. In the divalent kation which would be formed by addition of a proton to the second nitrogen atom, there would be no possibility of resonance and the increase in stability would disappear. That thio-urea forms salts by the addition of the proton to the sulphur atom and not to a nitrogen atom receives strong support from the fact that in acid solution thio-urea is readily oxidized to a compound containing the linking —S—S—, which is known to be a characteristic property of the —SH group.[3]

Objections have been raised against the zwitterion structure for urea, but of these only two call for any remark. The first is raised by E. J. Cohn, T. L. McMeekin, J. T. Edsall, and M. H. Blanchard:[4] they observed that the ratio of the solubility in alcohol to that in water for any substance is much affected by whether it is a zwitterion or not; notably amino-acids, where the zwitterion structure is beyond dispute, show very small values for this ratio. This is, of course, to be expected, since a zwitterion, being essentially ionic in nature although not an electrolyte, would behave like a salt and show an abnormally high solubility in water and an abnormally low one in less polar solvents. They found that the ratio for urea is much larger than for the amino-acids and hence conclude that the zwitterion structure is absent. Such an argument overlooks one possibility in the structure of urea. In addition to the resonance between the nitrogen atoms in the zwitterion formula, there may well be resonance between that zwitterion structure and the true diamide structure, so that urea itself may be a resonance-hybrid of the two forms

$$\overset{-}{O}\text{—}C\!\!\begin{matrix} {}^{\diagup}NH_2 \\ {}_{\overset{+}{\diagdown}NH_2} \end{matrix} \quad \text{and} \quad O:C\!\!\begin{matrix} {}^{\diagup}NH_2 \\ {}_{\diagdown NH_2} \end{matrix}$$
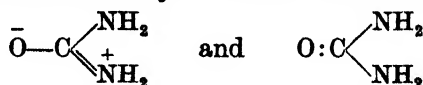
[1] E. A. Werner, J.C.S. 1914, 105, 923.   [2] H. Lecher, Annalen, 1924, 438, 169.
[3] H. Lecher, loc. cit.   [4] J. biol. Chem. 1933, 100, Proc. xxviii.

If this is so, the actual structure of urea will depend on its environment, because the contribution which each of the above two structures makes to the hybrid will be affected by the fields of force of the surrounding molecules. In the solid state the evidence seems conclusive that the contribution of the zwitterion is by far the more important, but in alcoholic solution the position may be reversed. In this event urea as a solute in alcohol would behave more as though it had the uncharged diamide structure, and would not show the characteristically low solubility of a salt. The state of affairs with an amino-acid is quite different, the zwitterion form and the uncharged forms are not interconvertible by a shift in the distribution of electrons, but by the migration of a proton, and there is no possible resonance between them:

$$\overset{+}{N}H_3 \cdot CH_2 \cdot CO_2^- \longrightarrow NH_2 \cdot CH_2 \cdot CO_2H.$$
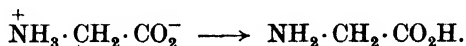
Whether an amino-acid exists in the zwitterion or the uncharged form is determined by the dissociation constants of its amino and carboxyl groups (see p. 111).

The solubility measurements cannot therefore be regarded as disproving the possibility that in certain states urea is an internal salt, but they do indicate that it does not behave as such under all conditions, and that its actual structure is a function of its environment. Such a conception is supported by the behaviour of the substituted ureas and thio-ureas. Although there is ample evidence that urea as a solid is a resonance-hybrid in which the zwitterion structure predominates, no one would suggest that a substitution product such as $S:C(NMe_2)_2$ is an internal salt. Its melting-point is 78° (thio-urea m.p. 180°), and it boils undecomposed at 245°.[1] A more probable view is that the ureas and the thio-ureas are resonance-hybrids, and that the predominance of the two contributing structures is determined both by the nature of the substituents present and also by external conditions such as the solvent.

The second objection to the zwitterion structure for thio-urea has been raised by H. Lecher,[2] who considered it so overwhelming that he abandoned the structure, though he himself had been one of the first to put it forward. Lecher argued that if thio-urea is an internal salt·the molecule must contain an acidic and a basic portion: if then we introduce a substituent into the basic portion of such a nature as to suppress the basicity completely, the resulting molecule should be acidic. The example he dealt with was N,N'-diacetylthio-urea: we know that the acetyl groups, one on each nitrogen atom, will suppress the basicity, hence the compound should be markedly acidic, while in fact it is completely neutral. The argument has been well answered by F. Arndt,[3] who points out that the argument is founded on a behaviour of amino-acids which clearly cannot be expected to occur in thio-urea. An amino-acid, e.g. glycine, is a neutral molecule, but N-acetylglycine is a true carboxylic acid: if one thinks of introducing

[1] M. Delépine, *Bull. Soc. chim.* 1910, [iv], **7**, 991.
[2] *Annalen*, 1927, **456**, 192.   [3] *Ber.* 1930, **63**, 2966, footnote.

the acetyl group into glycine in its zwitterion form, one gets the molecule $CH_3 \cdot CO \cdot \overset{+}{N}H_2 \cdot CH_2 \cdot CO_2^-$. Now we know that the acetylated nitrogen atom cannot remain in this state, its basicity is too small: the only possibility is for the molecule to become $CH_3 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H$, which is a true acid. Applying the same reasoning to thio-urea shows that it is by no means necessary for the final product to be an acid: the substituted zwitterion is (XVI), and a change must occur which will remove the

$$
\begin{array}{cc}
\begin{array}{l} CH_3 \cdot CO \cdot NH \\ \\ CH_3 \cdot CO \cdot \overset{+}{N}H \end{array}\!\!\!\!\Big\rangle C\!-\!S^- & \begin{array}{l} CH_3 \cdot CO \cdot NH \\ \\ CH_3 \cdot CO \cdot NH \end{array}\!\!\!\!\Big\rangle C\!=\!S \\
\text{XVI.} & \text{XVII.}
\end{array}
$$
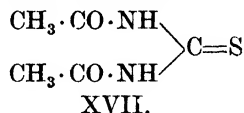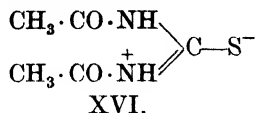
positive charge from the nitrogen atom. This can well be the change into (XVII), a neutral substance, and there is no need for the migration of a proton to give an acidic product: in the thio-urea molecule there is a possibility of a transition which is absent in the amino-acid molecule.

In conclusion it may be pointed out that it has often been stated that in solution thio-urea is a tautomeric mixture of (XVIII) and (XIX), because of reactions which seem to indicate the presence of the thiol

$$
\begin{array}{ccc}
\begin{array}{l} H_2N \\ \\ H_2N \end{array}\!\!\!\!\Big\rangle C\!=\!S & \begin{array}{l} H_2N \\ \\ HN \end{array}\!\!\!\!\Big\rangle C\!-\!SH & \begin{array}{l} H_2N \\ \\ H_2\overset{+}{N} \end{array}\!\!\!\!\Big\rangle C\!-\!S^- \\
\text{XVIII.} & \text{XIX.} & \text{XX.}
\end{array}
$$
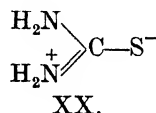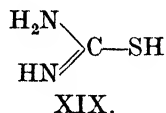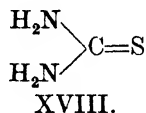
group —SH, e.g. the oxidation to —S—S— and the ready introduction of alkyl and acyl groups on to the sulphur atom. There is no direct evidence of tautomerism in solution, and it may well be that there is no tautomerism. All the reactions from which tautomerism has been deduced receive a perfectly natural explanation on the basis of the zwitterion formula (XX).

Substituted Ureas

Nitroso-urea is not known, but nitro-urea, $H_2N \cdot CO \cdot NH \cdot NO_2$, can be readily prepared and is stable as a solid if not in contact with soft glass or other weakly alkaline substances. If urea nitrate is treated with cold concentrated sulphuric acid, nitro-urea is formed,[1] and can be obtained by recrystallization from ether, benzene, or chloroform as colourless crystals melting at 159°.[2] It decomposes readily in hot aqueous solution and thus cannot be obtained pure by recrystallization from water. Its decomposition in water is accelerated by the presence of bases: the chief primary products are nitramide, $NH_2 \cdot NO_2$, and cyanic acid, from which nitro-urea can be synthesized at 0°, but these themselves decompose, the former giving nitrous oxide and water. Nitro-urea is nearly four times

$$ H_2N \cdot CO \cdot NH \cdot NO_2 \longrightarrow HNCO + NH_2 \cdot NO_2 $$
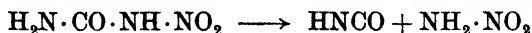
[1] J. Thiele and A. Lachman, *Annalen*, 1895, **288**, 281; T. L. Davis and K. C. Blanchard, *J. Amer. C. S.* 1929, **51**, 1790.

[2] R. Willstätter and A. Pfannenstiel, *Ber.* 1926, **59**, 1870.

as strong an acid as acetic acid and most probably exists in the isonitro form, $H_2N \cdot CO \cdot N:NO \cdot OH$. If its aqueous solution is mixed with a primary or secondary amine, nitrous oxide is evolved from the nitramide formed in the decomposition and the residual cyanic acid unites with the amine to give a substituted urea. This method of obtaining mono- and N,N-di-substituted ureas has the marked advantage that all the other products of the reaction are gaseous and the separation of the urea is thus much simplified.[1]

On reduction of nitro-urea, either by zinc in acid solution or electrolytically,[2] amino-urea is formed: the compound is usually called semicarbazide and in America semicarbazine. It forms colourless crystals melting at 96° and behaves as a monacidic base: its aqueous solution shows a neutral reaction but it forms well-characterized salts. Its structure is shown by the reduction method of preparation and by the facts that it can be obtained by the interaction of hydrazine hydrate and urea at 100°,[3] or better in solution in amyl alcohol,[4] and by the interaction of hydrazine and cyanic acid: the latter is a normal Wöhler urea preparation with hydrazine in the place of ammonia.

As a hydrazine derivative, since it can be described as the hydrazide of carbamic acid, semicarbazide will reduce Fehling's solution and silver oxide. A more important point is that, like other hydrazine derivatives, it will condense with compounds containing a carbonyl group with elimination of water to give semicarbazones:

$$H_2N \cdot CO \cdot NH \cdot NH_2 + O:CRR' \longrightarrow H_2N \cdot CO \cdot NH \cdot N:CRR'.$$
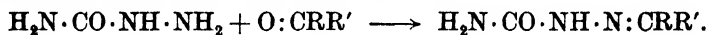
These compounds usually crystallize well and are not very soluble, and they can be hydrolysed by aqueous acids to the original carbonyl compound. They are thus extremely useful for the identification and separation of aldehydes and ketones and in some cases are more useful than phenylhydrazones. To prepare them it is usually sufficient to shake the aldehyde or ketone with a warm aqueous solution of semicarbazide hydrochloride and sodium acetate, although some aldehydes will react even in the presence of much free hydrochloric acid.[5] Solutions of semicarbazide decompose slowly on keeping or on heating to form the amide of hydrazine dicarboxylic acid, $H_2N \cdot CO \cdot NH \cdot NH \cdot CO \cdot NH_2$:[6] this substance, which is sparingly soluble and melts at 245°, has often been mistaken for a semicarbazone when semicarbazide solutions have been boiled for several hours. The rate of formation and the ease of hydrolysis of a semicarbazone bear no relationship to one another:[7] in general aldehydes react more

[1] T. L. Davis and K. C. Blanchard, loc. cit.

[2] G. N. F. Holroyd, *J.C.S.* 1901, **79**, 1326; L. J. Bircher, A. W. Ingersoll, B. F. Armendt, and G. Cook, *J. Amer. C. S.* 1925, **47**, 391.

[3] T. Curtius and K. Heidenrech, *Ber.* 1894, **27**, 56.

[4] S. M. Mistry and P. C. Guha, *J. Ind. C. S.* 1930, **7**, 793.

[5] A. Michael, *J. Amer. C. S.* 1919, **41**, 393.

[6] J. Thiele, *Annalen*, 1892, **271**, 127.

[7] J. B. Conant and P. D. Bartlett, *J. Amer. C. S.* 1932, **54**, 2881.

rapidly than ketones to form semicarbazones and the semicarbazones of aldehydes are more stable than those of ketones, but no simple generalization is possible.

Since they contain the group $\diagup C{=}N{-}$, semicarbazones of aldehydes and unsymmetrical ketones would be expected to exist in two geometrically isomeric forms. This expectation is fulfilled, and in many cases, as with phenyl hydrazones, the two isomers are known:[1] no general method of discovering the configurations of these isomers is, however, known.

Two chlorine substitution products of urea are known. If chlorine is passed through a cooled aqueous solution of urea until the quantity absorbed corresponds to monosubstitution, on standing and further cooling monochlorurea, $H_2N \cdot CO \cdot NHCl$, melting at 71°, crystallizes out.[2] If the passage of chlorine is continued, dichlorurea, $OC(NHCl)_2$, melting at 83°, crystallizes out:[3] the yield of the latter compound is increased if zinc oxide is added, since the hydrogen chloride formed combines with this and hydrolysis of the product is prevented. The two compounds are very similar in their behaviour, and decompose on keeping and more rapidly in solution. They show the typical reactions of compounds containing halogen united to nitrogen and act as oxidizing agents, liberating iodine, for example, from solutions of iodides. The dichloro compound acts as a chlorinating agent on many compounds, particularly in acid solution, and it can be used as such for preparative purposes.[4]

Cyano-urea, $H_2N \cdot CO \cdot NH \cdot CN$, which can also be described as the ureide of cyanic acid or the nitrile of allophanic acid (urea carboxylic acid), can be obtained either by the partial hydrolysis by lime water or baryta of 'dicyandiamide', which is the polymerization product of cyanamide and is really cyano-guanidine, $H_2N \cdot C({:}NH) \cdot NH \cdot CN$, or better by the interaction of cyanamide and potassium cyanate. The latter is a normal Wöhler urea synthesis in which cyanamide, $H_2N \cdot CN$, replaces ammonia. The compound is a strong acid, a fact suggesting that it exists in solution in a tautomeric form other than that given above. It can be hydrolysed by acids to biuret.

The alkyl and aryl derivatives of urea can be divided into two groups, the N-derivatives, in which the hydrocarbon radical or radicals are attached to nitrogen, and the O-derivatives, in which a hydrocarbon radical is attached to oxygen, the structure being derived from the so-called iso-form of urea, $H_2N \cdot C({:}NH) \cdot OH$. The N-derivatives can be obtained by the following methods, among others:

(i) The extension of Wöhler's synthesis: if cyanic acid interacts with

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[1] See *Stereochemie* [1932–3], ed. K. Freudenberg, J. Meisenheimer, and W. Theilacker, p. 1101; a particularly interesting case is that of the optically active semicarbazone of 4-methylcyclohexanone, W. H. Mills and A. M. Bain, *J.C.S.* 1914, **105**, 64.   [2] A. Behal and A. Detoeuf, *C.r.* 1911, **153**, 681.

[3] F. D. Chattaway, *Proc. Roy. Soc.* 1908, **81**, A, 381.

[4] M. W. Lichoscherstov and W. I. Tzimbalist, *J. Gen. Chem. Russ.* 1933, **3**, 162; *Zent.* 1934, i. 1476.

primary or secondary amines, mono-substituted ureas or unsymmetrical di-substituted ureas are formed. The symmetrically (N,N') di-substituted ureas are formed by the action of amines on the esters of cyanic acid:

$$O:C:NEt + EtNH_2 \longrightarrow O:C(NHEt)_2.$$
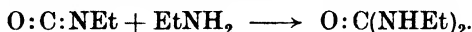
(ii) The action of secondary amines on carbonyl chloride gives the N-tetra-substituted ureas.

(iii) Symmetrical di-substituted ureas can be often obtained from urea itself by interaction with a primary amine. This reaction goes very smoothly with aromatic amines and the diphenyl urea can be made with great ease by heating together urea and aniline:

$$2\phi NH_2 + CO(NH_2)_2 \longrightarrow CO(NH\phi)_2 + 2NH_3.$$
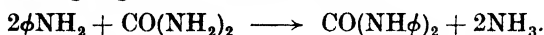
The best yields are obtained with acetic acid, or, a mixture of acetic acid and alcohol, as solvent: under these conditions aliphatic amines can be used.[1] Probably cyanic acid or an isocyanate is an intermediate.

The N-alkyl ureas present few points of interest: they are uniformly monacidic bases, melting at temperatures below that of urea. They are more stable to heat than urea and some can be distilled unchanged. Monomethyl urea is readily obtainable from technical methylamine hydrochloride and potassium cyanate and one of its derivatives affords the most convenient method for the preparation of diazomethane.[2] If methylurea is dissolved in dilute sulphuric acid and sodium nitrite added at a low temperature, crystals of nitrosomethylurea, $H_2N \cdot CO \cdot N(NO) \cdot CH_3$, separate.[3] This compound melts with decomposition at 121° and is insoluble in cold water; it is comparatively stable at room temperature, although on summer days it is best kept in an ice-chest. On hydrolysis with alkalis it breaks down quantitatively into a cyanate and diazomethane:

$$H_2N \cdot CO \cdot N(NO) \cdot CH_3 + NaOH \longrightarrow CH_2N_2 + NaOCN + 2H_2O.$$
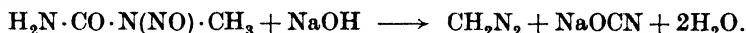
This method of obtaining diazomethane is a marked improvement on the older method in which nitrosomethylurethane was used, since the materials needed are more readily obtained (see p. 347).

The O-substituted ureas are oils or low-melting solids which are formed either by the method of J. Stieglitz or that of E. A. Werner. In the former, cyanamide in excess of an anhydrous alcohol is treated with dry hydrogen chloride: on removal of the excess alcohol the hydrochloride of the iso-urea remains:[4]

$$H_2N \cdot C \equiv N + ROH \longrightarrow H_2N \cdot C(:NH) \cdot OR.$$

Werner's method[5] has already been referred to and consists in treating urea with methyl sulphate: from the reaction mixture O-methylurea can

[1] A. Sonn, *Ber.* 1914, **47**, 2437.

[2] E. A. Werner, *J.C.S.* 1919, **115**, 1093; F. Arndt and J. Amende, *Z. angew. Chem.* 1930, **43**, 444; F. Arndt and H. Scholz, ibid. 1933, **46**, 47.

[3] G. v. Brüning, *Ber.* 1888, **21**, 1809.

[4] R. H. McKee, *Amer. Chem. J.* 1901, **26**, 209.   [5] *J.C.S.* 1914, **105**, 923.

be separated. These iso-ureas are difficult to deal with because they are often hygroscopic and crystallize slowly: their salicylates, however, are usually easily purified.[1] They contain the amidine grouping $-C\begin{smallmatrix} NH_2 \\ NH \end{smallmatrix}$ and hence are fairly strong monacidic bases: their dissociation constants are roughly of the same magnitude as those of primary aliphatic amines and are considerably larger than those of urea or its N-substitution products.[2]

The acyl derivatives of urea such as acetyl urea again fall into the two classes of N- and O-derivatives. The former class are often referred to as ureides, and N-acetyl urea can equally well be called the ureide of acetic acid. The ureides of monobasic acids are not of much interest, but with dibasic acids such as oxalic or malonic acids, urea forms cyclic ureides, in which both its nitrogen atoms are united to a carboxylic residue: examples are the ureide of oxalic acid, which is usually called parabanic acid, and that of malonic acid called barbituric acid.

$$\begin{matrix} CO\text{---}NH \\ | \quad\quad\ \ >CO \\ CO\text{---}NH \end{matrix} \qquad\qquad \begin{matrix} \quad CO\text{---}NH \\ CH_2 \quad\quad\quad >CO \\ \quad CO\text{---}NH \end{matrix}$$
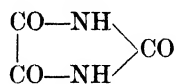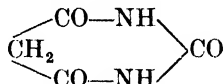
Parabanic acid Barbituric acid

These cyclic ureides were first obtained as degradation products of uric acid and other members of the purine group, and their chemistry is intimately connected with the chemistry of that group.

Thio-urea

Thio-urea, $S:C(NH_2)_2$, the sulphur analogue of urea, can be obtained from ammonium thiocyanate by an isomeric change analogous to that of ammonium cyanate, but the relationship between the two substances is very different from that between urea and ammonium cyanate. Below 100° the rate of change of ammonium thiocyanate into thio-urea is unobservably small: at temperatures between 140° and 180° equilibrium between the two compounds is set up fairly fast, but thio-urea is present only to an extent of about 25 per cent. in the equilibrium mixture. The equilibrium concentrations at a series of temperatures have been measured by A. N. Kappanna[3] who showed that the equilibrium shifts in favour of ammonium thiocyanate as the temperature is increased, the mixture containing 28·1 per cent. of thio-urea at 140° and 21·8 per cent. at 180°. His results indicate that the heat of transformation of ammonium thiocyanate into this urea is 3·17 kg. cal. per gramme molecule. The rates of reaction in both directions seem to be unimolecular both in absence of a solvent[4]

[1] S. Basterfield and E. C. Powell, *Canad. J. Res.* 1929, **1**, 261.

[2] S. Basterfield and J. W. Tomecko, ibid. 1933, **8**, 458.

[3] *J. Ind. C. S.* 1927, **4**, 217.

[4] Kappanna, loc. cit.; W. R. G. Atkins and E. A. Werner, *J.C.S.* 1912, **99**, 1167.

and in solution in ethylene glycol.[1] In order to prepare thio-urea, ammonium thiocyanate is heated rapidly to 160–170° for a short time, and then poured into cold water: on evaporation a solid separates which is a compound of thio-urea and ammonium thiocyanate and seems to have the composition $4CS(NH_2)_2,NH_4CNS$: this compound when dissolved in water deposits pure thio-urea, which unlike urea is sparingly soluble in cold water. Thio-urea has no true melting-point because of the rapidity of the isomeric change into ammonium thiocyanate, but on rapid heating appears to melt at 179°. If heated *in vacuo*, it sublimes as ammonium thiocyanate. It has none of the physiological interest of urea, but has been found to occur in the free state in the laburnum.[2] Its crystal structure has been investigated by R. W. G. Wyckoff and R. B. Corey.[3]

Thio-urea is neutral in reaction, but reacts towards acids as a monacidic base, forming comparatively stable salts. It will also react readily with alkyl and aryl halides to give the salt of an S-substituted thio-urea: thus with methyl iodide, S-methylthio-urea hydriodide (I) is formed.

I. $\begin{array}{c} H_2N \\ ^+ \\ H_2N \end{array} \!\!\! \Big\rangle C\!-\!SMe\ [I]^-$ II. $\begin{array}{c} H_2N \\ ^+ \\ H_2N \end{array} \!\!\! \Big\rangle C\!-\!S^-$
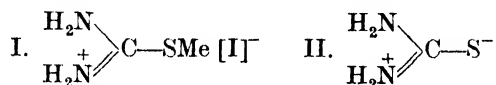
As has been mentioned above, this suggests that the normal state of thio-urea is that of the zwitterion (II). This deduction is supported by the action of oxidizing agents on thio-urea: neutral reagents, such as permanganate in the absence of acid, give, as the main oxidation product, urea, but in the presence of a mineral acid nearly every oxidizing agent gives a salt of formamidine disulphide (III), a typical product of the oxidation of a compound containing the thiol (—SH) group. This again

III. $\begin{array}{c} H_2N \\ HN \end{array} \!\!\! \Big\rangle C\!-\!S\!-\!S\!-\!C\!\! \Big\langle \begin{array}{c} NH_2 \\ NH \end{array}$ IV. $\begin{array}{c} H_2N \\ ^+ \\ H_2N \end{array} \!\!\! \Big\rangle C\!-\!SH$
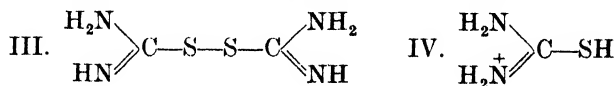
suggests that thio-urea in the presence of acids is the kation (IV) derived from the zwitterion (II). The same oxidation to formamidine disulphide is brought about quantitatively in solution by iodine if the thio-urea concentration does not exceed 0·02 per cent., and a method of volumetric analysis of thio-urea is based upon this.[4]

In order to explain the S-alkylation and the oxidation, it was formerly thought necessary to assume that thio-urea exists largely in the *iso*-form, $\begin{array}{c} H_2N \\ HN \end{array} \!\!\! \big\rangle C\!-\!SH$, and that in solution it is a tautomeric mixture. Though this possibility is not excluded, the facts receive a simpler and more probable explanation on the zwitterion structure of the molecule.

[1] W. Ure and T. B. Edwards, *Trans. Roy. Soc. Canada*, 1930, [3], **24**, Section III, 153.
[2] G. Klein and E. Farkass, *Österr. bot. Z.* 1930, **79**, 107.
[3] *Z. Krist.* 1932, **81**, 386.   [4] E. A. Werner, *J.C.S.* 1912, **101**, 2168.

As is the case of urea, the substitution products of thio-urea fall into two classes, the S- and the N-derivatives. Their methods of preparation present few points of interest; the more important are:

(i) Ammonia and amines react with the esters of isothiocyanic acid (mustard oils) to give N-alkyl thio-ureas:

$$S:C:NR + R' \cdot NH_2 \longrightarrow S:C\begin{smallmatrix} NHR \\ NHR' \end{smallmatrix}$$
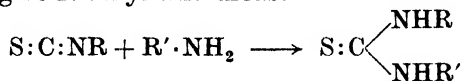
This reaction provides a good method for the detection of primary and secondary aliphatic amines. If α-naphthyl isothiocyanate is added to an alcoholic solution of such an amine, after a short period of heating the symmetrical alkyl-α-naphthylthio-urea can be obtained as a well-crystallized solid, the melting-point of which serves to identify the amine.[1] The advantage of this particular reagent is that the thio-ureas derived from it have melting-points within a suitable range and that this isothiocyanate does not react easily with water or alcohols.

(ii) Carbon disulphide reacts with aromatic primary amines (but not aliphatic) to give symmetrical di-N-aryl thio-ureas. The reaction is hastened by the presence of a catalyst such as free sulphur, hydrogen peroxide, caustic potash, pyridine, or iodine. The resultant aryl thio-ureas are also known as thiocarbanilides:

$$S:C:S + 2\phi \cdot NH_2 \longrightarrow S:C(NH\phi)_2 + H_2S.$$
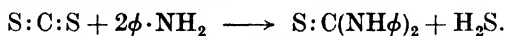
(iii) The S-derivatives are prepared by direct alkylation from thio-urea. The sulphate of S-methylthio-urea is sparingly soluble in cold water and can be very readily obtained by the interaction of thio-urea and dimethyl sulphate.[2] In hot alkaline solution it decomposes to methyl mercaptan and cyanamide which polymerizes to dicyanodiamide, and this is the only satisfactory method known for the preparation of methyl mercaptan.

Thio-urea forms molecular compounds, often of great stability, with a wide variety of inorganic salts, and not only with salts of metals such as copper which form co-ordination compounds with great ease, but also with salts such as potassium iodide and caesium chloride. The constitution of these latter complexes is unknown; similar compounds are formed both by amides (e.g. acetamide) and by amino-acids (e.g. glycine).[3]

Carbodiimides

These compounds are substitution derivatives of the diimide of carbonic acid, $HN=C=NH$, which itself is unknown and is isomeric with cyanamide $N\equiv C \cdot NH_2$. Few of these compounds have been prepared; they are extremely reactive and also polymerize on standing to insoluble resinous products. Two methods of preparation are known:

(i) If yellow mercuric oxide is added to a solution of a symm.-di-

[1] C. M. Suter and E. W. Moffett, *J. Amer. C. S.* 1933, **55**, 2497.

[2] F. Arndt, *Ber.* 1921, **54**, 2236.

[3] See P. Pfeiffer, *Organische Molekülverbindungen*, Stuttgart, 1927, p. 166.

substituted thio-urea in dry benzene, a carbodiimide is formed together with a certain amount of the corresponding di-substituted urea:

$$S:C\begin{cases}NHR\\NHR\end{cases} \longrightarrow RN:C:NR + H_2S.$$
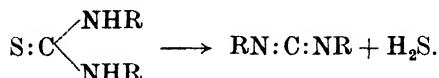
The product is separated by removal of the benzene and distilling the residue *in vacuo*. By this means dipropyl-carbodiimide, a liquid boiling at 80°/20 mm., was prepared by F. Chancel,[1] and diphenyl-carbodiimide, boiling-point 163°/11 mm., by W. Weith.[2]

(ii) Diethyl-carbodiimide was obtained by H.Staudinger[3] by the action of ethyl isothiocyanate, ethyl isocyanate, or carbon dioxide on triethylphosphine ethylimine. The latter, formed by loss of nitrogen from the addition product of triethylphosphine and ethyl azide, has the structure $Et_3P:N\cdot Et$ and reacts with compounds containing the group $>C:O$ or $>C:S$ to form Et_3PO or Et_3PS. Thus ethyl isocyanate $EtN:C:O$ gives the phosphine oxide and the carbodiimide. Carbon dioxide gives the same product because its first action is to form ethyl isocyanate, which then reacts as before. This diethyl carbodiimide is the simplest known and is a colourless liquid boiling at 24·5°/11 mm. The diphenyl compound can be prepared by a similar method.

The main chemical characteristic of the carbodiimides is the ease with which they enter into addition reactions. In aqueous alcohol in the presence of hydrogen chloride they take up the elements of water to give substituted ureas (I); with hydrogen sulphide they give substituted thio-ureas, and with aniline derivatives of phenyl guanidine (II).

$$I.\ RN:C:NR + H_2O \longrightarrow O:C(NHR)_2$$

$$II.\ RN:C:NR + \phi NH_2 \longrightarrow \phi NH\cdot C\begin{cases}NR\\NHR\end{cases}$$
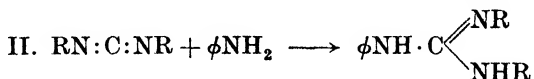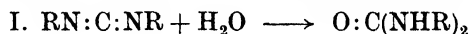
Carbo-diphenylimide reacts readily with aliphatic diazo compounds and with hydrazoic acid. With diazomethane the product is 1-phenyl-5-anilino-(1, 2, 4)-triazole (III),[4] and with hydrazoic acid, 1-phenyl-5-anilino-tetrazole (IV).[5]
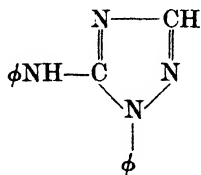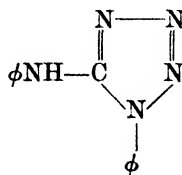
III.   IV.

On standing, the carbodiimides polymerize, the aromatic derivatives much

[1] *C.r.* 1893, **116**, 330.   [2] See R. Rotter, *Monats.* 1926, **47**, 353.
[3] *Helv. Chim. Acta.* 1921, **4**, 881.   [4] R. Rotter, loc. cit.
[5] R. Stollé, *Ber.* 1922, **55**, 1289; E. Olivieri-Mandalà, *Gazz.* 1922, **52**, ii, 139.

more readily than the aliphatic. The diphenyl derivative gives a definite trimolecular polymer of melting-point 160–161°, which regenerates the monomolecular compound on heating: the behaviour recalls that of cyanuric acid, and this polymer probably has a cyclic structure analogous to that of cyanuric acid.

$$
\begin{array}{c}
\text{N}\phi \\
\parallel \\
\text{C} \\
\phi\text{—N} \qquad \text{N—}\phi \\
\phi\text{N}=\text{C} \qquad \text{C}=\text{N}\phi \\
\text{N} \\
\mid \\
\phi
\end{array}
$$
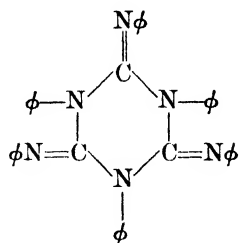
There seems also to be an amorphous polymer, about which little is known. An interesting stereochemical point arises in connexion with the carbodiimides. If we think of the space arrangement of the molecule RN:C:NR and apply to it our knowledge of the stereochemistry of the oximes, it is clear that the molecule cannot be symmetrical since the configuration of each half is (V) and not the symmetrical arrangement (VI).

$$
\text{V.} \begin{array}{c} \text{C} \\ \parallel \\ \text{N} \\ \diagdown \\ \text{R} \end{array} \qquad \text{VI.} \begin{array}{c} \text{C} \\ \parallel \\ \text{N} \\ \text{R} \end{array}
$$
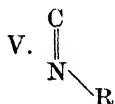
The central carbon atom and the two nitrogen atoms of a carbodiimide RN:C:NR must lie in one straight line because of the arrangement of the valencies about the carbon atom, but the planes of the two double bonds, to use a convenient but inaccurate phrase, must be at right angles to one another. The consequence of this must be that the two R groups, which cannot lie in the same line with the carbon and nitrogen atoms, will be joined to their nitrogen atoms by valencies which are in planes at right angles to one another, so that the space arrangement of the molecule cannot be represented in two dimensions. Two such arrangements are possible, and these are enantiomorphous, even if the two R groups are identical. An attempt is made to show them in the following formulae (VII and VIII), in which thin lines are bonds lying in the plane of the page, thick lines are those which run forward from that plane, and dotted lines those which run backward from that plane.

$$
\begin{array}{ccc}
\overset{\displaystyle \diagup \text{R}}{\underset{\displaystyle \text{R}\diagup}{\text{NOC}\odot\text{N}}} & \overset{\displaystyle \text{R}\diagdown}{\underset{\displaystyle \text{N}}{\text{N}\odot\text{C}\odot\text{N}}} & \overset{\displaystyle \text{R}\diagdown \qquad \diagup\text{R}}{\text{NOC}\odot\text{N}} \\
\text{VII.} & & \text{VIII.}
\end{array}
$$
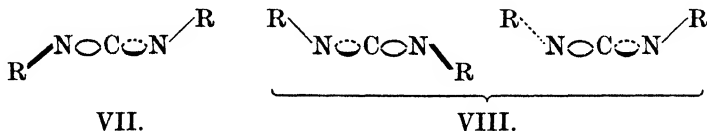
On these grounds it would be expected that a carbodiimide should exist in optically active forms. Attempts to detect this asymmetry of the molecule by obtaining an optically active compound were defeated by the

difficulties of dealing with such reactive and unstable substances.[1] The lack of symmetry in the molecule is, however, clearly demonstrated by the fact that both diphenyl- and di-p-tolyl-carbodiimides have finite electric moments ($\mu = 1\cdot89$ D and $1\cdot96$ D, respectively) and thus contain no centre of symmetry.[2]

Guanidine

Guanidine, $HN:C(NH_2)_2$, is the imide of urea or the amidine of carbamic acid. In the free state it occurs in nature only in a few plants, but its derivatives are widely distributed and are of great physiological importance, especially in the action of muscular tissue. Its constitution is shown by a variety of syntheses such as the action of ammonia on carbonyl chloride or ethyl orthocarbonate, $C(OEt)_4$, the reduction of tetranitromethane with hydrochloric acid and zinc,[3] and the addition of ammonia to cyanamide: $N:C\cdot NH_2 \longrightarrow HN:C(NH_2)_2$.

Guanidine is a readily obtainable substance since it can be prepared from technical calcium cyanamide. The latter on heating with water gives dicyandiamide by polymerization of the cyanamide and this on fusing with an ammonium salt gives very good yields of the salt of guanidine.[4] J. S. Blair and J. M. Braham[5] have studied the course of the reaction by extracting samples during its progress and analysing them, and have shown that the ammonia first reacts with the dicyandiamide to give biguanide (the guanidine analogue of biuret) which is decomposed by more ammonia to give two molecules of guanidine.

$$HN:C{\Large\langle}_{NH_2}^{NH\cdot CN} \xrightarrow{NH_3} \ _{H_2N}^{HN}{\Large\rangle}C{\Large\langle}_{}^{NH}\ _{}^{}C{\Large\langle}_{NH_2}^{NH} \xrightarrow{NH_3} 2\,HN:C{\Large\langle}_{NH_2}^{NH_2}$$
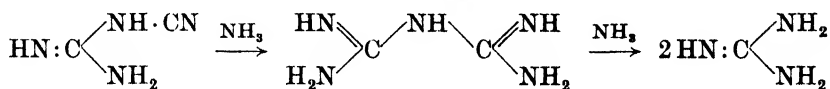
Another method for preparing guanidine from calcium cyanamide is to heat it with dilute sulphuric acid to form dicyandiamidine; this compound, if treated in boiling water with a stream of carbon dioxide, gives a theoretical yield of guanidine carbonate:[6]

$$HN:C{\Large\langle}_{NH_2}^{NH\cdot CO\cdot NH_2} \longrightarrow HN:C{\Large\langle}_{NH_2}^{NH_2} + CO_2 + NH_3.$$
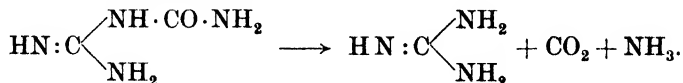
The method employed before cyanamide and its derivatives were so readily obtainable was to heat ammonium thiocyanate to 180–185° for about twenty hours. The residue then contains large quantities of guanidine thiocyanate. The reaction proceeds in several stages; the thio-urea formed by isomeric change of some ammonium thiocyanate

[1] L. J. Rolls and R. Adams, *J. Amer. C. S.* 1932, **54**, 2494.

[2] E. Bergmann and W. Schütz, *Z. phys. Chem.* 1932, B, **19**, 389.

[3] J. N. Rakshit, *J. Amer. C. S.* 1914, **36**, 1221; A. Stähler, *Ber.* 1914, **47**, 909.

[4] E. A. Werner and J. Bell, *J.C.S.* 1920, **117**, 1133; T. L. Davis, *J. Amer. C. S.* 1921, **43**, 2234.

[5] Ibid. 1922, **44**, 2342.   [6] E. Merck, D.R.-P. 1926, 458437.

decomposes into hydrogen sulphide and cyanamide: the latter combines with more ammonium thiocyanate to the salt of guanidine, while the hydrogen sulphide combines with unchanged ammonium thiocyanate to give ammonium trithiocarbonate, the other chief product :

$$NH_4CNS \longrightarrow CS(NH_2)_2 \longrightarrow H_2S + N\!:\!C\cdot NH_2$$
$$N\!:\!C\cdot NH_2 + NH_3 \longrightarrow (H_2N)_2C\!:\!NH$$
$$NH_4S\cdot CN + 2H_2S \longrightarrow S\!:\!C(SNH_4)_2.$$
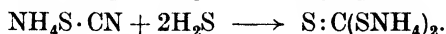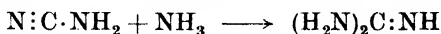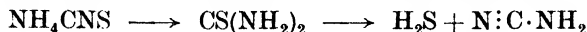
The salts of guanidine can readily be obtained pure, especially the carbonate which crystallizes well; but the free base is not so easy to prepare. One method that has been used is to mix alcoholic solutions of guanidine perchlorate and potassium hydroxide, remove the insoluble potassium perchlorate, and evaporate the solvent *in vacuo* over phosphorus pentoxide.[1] It forms colourless, caustic, and very hygroscopic crystals that melt indistinctly at 50° and decompose at a higher temperature to give melamine, the tripolymer of cyanamide (see p. 344). It is stable in aqueous solution and is a monacid base almost as strong as the caustic alkalis. It forms stable salts even with weak acids such as boric and silicic acids.

The structure of the guanidine kation has been clearly shown by H. Lecher and F. Graf[2] to be (I) and not (II).

$$\text{I. } H_2\overset{+}{N}\!=\!C\!\!\left\langle\begin{array}{l}NH_2\\NH_2\end{array}\right. \qquad \text{II. } HN\!=\!C\!\!\left\langle\begin{array}{l}NH_3^+\\NH_2\end{array}\right. \qquad \text{V. } O\!=\!C\!\!\left\langle\begin{array}{l}O^-\\O^-\end{array}\right.$$
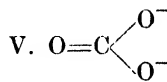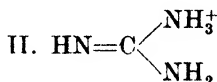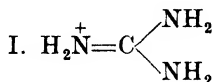
By purely chemical methods it is obviously impossible to distinguish between (I) and (II), but if the alkyl guanidines are used, which are similar in behaviour to guanidine in every respect, the distinction becomes possible. Lecher and Graf prepared N,N,N′,N′-tetramethyl-N″-ethyl-guanidine (III) and also pentamethyl guanidine (IV). The first they allowed to combine with methyl iodide to give a pentalkyl guanidinium iodide and the latter with ethyl iodide.

If now the kation structure is of the type shown in (II), the two salts should be different; if, on the other hand, it is of the type shown in (I), they should be identical, and this identity was established experimentally.

Type I   Type II

$$Et Me\overset{+}{N}\!=\!C\!\!\left\langle\begin{array}{l}NMe_2\\NMe_2\end{array}\right.[I]^- \xleftarrow{MeI} EtN\!=\!C\!\!\left\langle\begin{array}{l}NMe_2\\NMe_2\end{array}\right. \xrightarrow{MeI} EtN\!=\!C\!\!\left\langle\begin{array}{l}\overset{+}{N}Me_3\\NMe_2\end{array}\right.[I]^-$$

III.
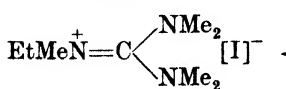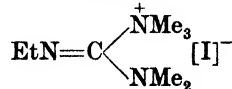
$$Et Me\overset{+}{N}\!=\!C\!\!\left\langle\begin{array}{l}NMe_2\\NMe_2\end{array}\right.[I]^- \xleftarrow{EtI} MeN\!=\!C\!\!\left\langle\begin{array}{l}NMe_2\\NMe_2\end{array}\right. \xrightarrow{EtI} MeN\!=\!C\!\!\left\langle\begin{array}{l}\overset{+}{N}Me_2Et\\NMe_2\end{array}\right.[I]^-$$
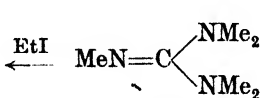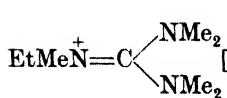
IV.
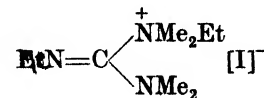
[1] W. Marckwald and F. Struwe, *Ber.* 1922, **55**, 458.
[2] *Annalen*, 1924, **438**, 154; 1925, **445**, 61.

The state of the three nitrogen atoms in the guanidinium ion (I) is similar to that of the two nitrogen atoms in an amidine kation already discussed: there is no true difference between the three atoms and the kation is a resonance-hybrid, just as is the very closely analogous carbonate anion (V). This is shown clearly in the crystalline structure of guanidinium iodide.[1] X-ray analysis of the positions of the atoms in the lattice shows that the three nitrogen atoms are symmetrically placed round the carbon atom, each at a distance of 1·18 A from it, and that the whole kation lies in one plane. The distance between the nitrogen atoms and the carbon atoms is even less than for a normal double bond (N—C, 1·48; N=C, 1·28; N≡C, 1·14 A); this must be due to the fact that all three nitrogen atoms are taking part in the resonance.

Guanidine can be hydrolysed to urea by baryta. Its nitrate is converted by strong sulphuric acid into nitroguanidine, $NH:C(NH_2)\cdot NH\cdot NO_2$, which is both acidic and basic and occurs in two polymorphic forms, both of which melt with decomposition at 246°.[2] The substance can be detonated and is used to some extent as a constituent of explosives; its peculiarity is the low temperature produced by the explosion as compared with explosives such as dynamite.[3] Nitroguanidine can be reduced by zinc dust, first to nitrosoguanidine, $NH:C(NH_2)\cdot NH\cdot NO$, which is also weakly basic and acidic, and then to amino-guanidine which is strongly basic: this latter can also be readily obtained by the interaction of cyanamide (from its calcium derivative) and hydrazine hydrate:[4]

$$N:C\cdot NH_2 + NH_2\cdot NH_2 \longrightarrow NH:C(NH_2)\cdot NH\cdot NH_2.$$
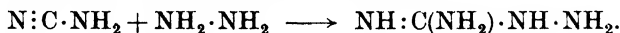
Being a hydrazine derivative, it condenses readily with ketones to give compounds analogous to semicarbazones, but with certain aromatic α-diketones, such as benzil, it gives amino-triazine derivatives.[5]
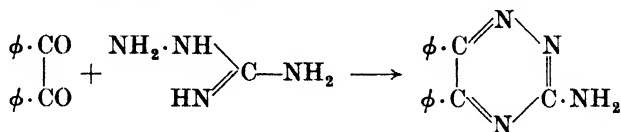
The alkyl guanidines are readily made by the action of alkylamines on cyanamide, or, more conveniently, by fusing together 'dicyanodiamide' with an alkylamine salt:[6] the reactions are analogous to the preparations of guanidine described above. Another convenient method is to treat S-methylthio-urea sulphate, which is easily made from thio-urea and dimethyl sulphate,[7] with a primary or secondary alkylamine when methyl

[1] W. Theilacker, *Z. Krist.* 1935, **90**, 51.
[2] T. L. Davis, A. A. Ashdown, and H. R. Couch, *J. Amer. C. S.* 1925, **47**, 1064; L. Desvergnes, *Rev. Chim. ind.* 1929, **38**, 265.
[3] P. Vieille, *Mém. Poudres*, 1901, **11**, 195.
[4] K. A. Hofmann and O. Ehrhart, *Ber.* 1911, **44**, 2713.
[5] J. Thiele and R. Bihan, *Annalen*, 1898, **302**, 299.
[6] E. A. Werner and J. Bell, *J.C.S.* 1922, **121**, 1790.
[7] F. Arndt, *Ber.* 1921, **54**, 2236.

mercaptan is evolved and very good yields of the alkylguanidine are obtained:[1]

$$\begin{matrix} H_2N \\ \\ HN \end{matrix}\!\!\!>\!C\!-\!SMe + H_2NR \longrightarrow \begin{matrix} H_2N \\ \\ HN \end{matrix}\!\!\!>\!C\!-\!NHR.$$
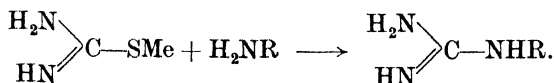
The monoalkyl guanidines are as strong bases as the parent substance, but the dialkyl derivatives are distinctly weaker.[2] Of the aryl derivatives, triphenylguanidine is the most important and is easily obtained by the interaction of thiocarbanilide and aniline, best in the presence of a substance such as litharge which will unite with the hydrogen sulphide formed :

$$\begin{matrix} \phi HN \\ \\ \phi HN \end{matrix}\!\!\!>\!C\!=\!S + H_2N\phi \longrightarrow \begin{matrix} \phi HN \\ \\ \phi HN \end{matrix}\!\!\!>\!C\!=\!N\phi + H_2S.$$
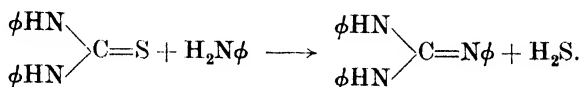
Guanidine and more especially certain derivatives of guanidine are of the greatest importance in certain physiological processes, particularly those of muscular action; for example the occurrence of certain types of tetanus is associated with the presence of guanidine and methylguanidine in the body, and tetanus can be caused by injecting these compounds.[3] Two acid derivatives are of importance, creatine, methylguanidine acetic acid, $H_2N \cdot C(:NH) \cdot NMe \cdot CH_2 \cdot CO_2H$, of which the phosphoric acid derivative is essential to the action of voluntary muscle,[4] and its internal amide, crea-

$$\text{tinine,} \quad \begin{matrix} CH_2\!-\!NMe \\ | \\ CO\!-\!\!-\!NH \end{matrix}\!\!\!>\!C\!:\!NH. \quad \text{The former is present in large amounts in mam-}$$

malian muscle, while the latter is excreted by mammals, especially during growth: both occur in the blood-stream. Their structure is shown by the synthesis of creatine from cyanamide and sarcosine (methylamino-acetic acid) and by the fact that creatinine is easily formed from creatine by boiling with water or dilute acids :

$$H_2N \cdot C\!:\!N + MeNH \cdot CH_2 \cdot CO_2H \longrightarrow H_2N \cdot C(:NH) \cdot NMe \cdot CH_2 \cdot CO_2H$$

$$\begin{matrix} CH_2\!-\!\!-\!NMe \\ | \\ COOH \; H_2N \end{matrix}\!\!\!>\!C\!:\!NH \longrightarrow \begin{matrix} CH_2\!-\!NMe \\ | \\ CO\!-\!\!-\!NH \end{matrix}\!\!\!>\!C\!:\!NH.$$
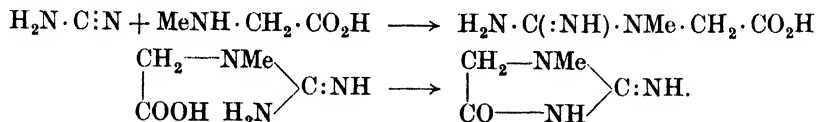
There is the possibility of three kinds of tautomerism in the molecule of creatinine: keto-enol, lactam-lactim, and imide-amide,[5]

$$\cdot CH_2 \cdot CO \cdot \rightleftharpoons \cdot CH\!:\!C(OH) \cdot$$
$$\cdot CO \cdot NH \cdot \rightleftharpoons \cdot C(OH)\!:\!N \cdot$$
$$\cdot HN \cdot C(:NH) \cdot \rightleftharpoons \cdot N\!:\!C(NH_2) \cdot$$
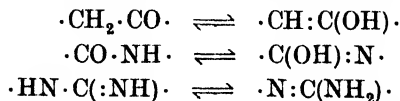
so that its actual structure is a somewhat complicated matter.

[1] R. Phillips and H. T. Clarke, *J. Amer. C. S.* 1923, **45**, 1755.

[2] T. L. Davis and R. C. Elderfield, *J. Amer. C. S.* 1932, **54**, 1502.

[3] D. N. Paton and L. Findlay, *Quart. J. Physiol.* 1916, **10**, 377.

[4] P. Eggleton and M. G. Eggleton, ibid. 1927, **63**, 155; C. H. Fiske and Y. Subbarow, *J. biol. Chem.* 1929, **81**, 629.

[5] H. R. Ing, *J.C.S.* 1932, 2047, 2198.

DERIVATIVES OF CYANOGEN

THE derivatives of cyanogen may be classified as follows:

I. The cyanides $R \cdot CN$ and isocyanides $R \cdot NC$.

II. The compounds containing the group $-(CNO)$. Representatives of four of the isomeric forms of this group are known:

(1) The derivatives of normal cyanic acid, HOCN.

(2) Those of isocyanic acid, HNCO.

(3) Fulminic acid HONC, its salts and derivatives.

(4) The nitrile oxides, $R \cdot CNO$.

In the first two of these groups the oxygen atom can be replaced by sulphur giving the derivatives of thiocyanic acid HSCN, and of isothiocyanic acid HNCS.

III. The tricyanogen derivatives. Many of the compounds of the above classes form triple polymers containing the tricyanogen ring.
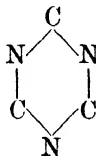
The first of the cyanogen compounds to be prepared was Prussian Blue, which was discovered by Diesbach at the beginning of the eighteenth century; but our real knowledge of their constitution dates from the work of J. E. Gay-Lussac in 1815. He showed that these bodies contain a radical composed of carbon and nitrogen which plays the part of an element. The radical resembles the halogens in several ways, especially in the formation of a hydracid and in the existence of free cyanogen, $(CN)_2$, analogous to chlorine, Cl_2.

Cyanogen, $(CN)_2$

There has been much doubt whether cyanogen can be synthesized from its elements by passing an electric discharge between carbon electrodes in an atmosphere of nitrogen. Since the heat of formation from the elements is known to be about -63 kg. cal.,[1] it is possible to calculate the fraction of nitrogen which must be converted into cyanogen at a series of temperatures: the compound being endothermic, its equilibrium percentage increases with temperature and above 2,000° is quite appreciable. Many investigators[2] have failed to detect any cyanogen under varying conditions of pressure and electric discharge, and have deduced either that it all

[1] J. McMorris and R. M. Badger, *J. Amer. C. S.* 1933, **55**, 1952.

[2] e.g. E. Briner and J. Deshusses, *Helv. Chim. Acta*, 1930, **13**, 629.

decomposes on passing out of the arc or that the calculations do not apply to the conditions ruling in the discharge. K. Peters, however,[1] has found that with high current-densities and fairly low pressures cyanogen is formed, and by circulating pure nitrogen through the discharge chamber and freezing out the condensable product has succeeded in converting the nitrogen quantitatively into cyanogen. Cyanogen is formed from active nitrogen and acetylene.[2] It occurs in small amount in coal-gas and in the gases from blast furnaces. It can be obtained in the laboratory by Gay-Lussac's method of heating mercuric cyanide or by mixing solutions of potassium cyanide and copper sulphate. In this last reaction cupric cyanide or a complex of this with the cyanide ion is first formed, and on warming breaks down into cyanogen and the cuprous compound, just as cupric iodide gives free iodine and cuprous iodide.

Two chemical methods of formation are a clear indication of its constitution: the dehydration of ammonium oxalate or oxamide with phosphorus pentoxide and of glyoxime (the dioxime of glyoxal) with acetic anhydride.

$$H_2N \cdot CO \cdot CO \cdot NH_2 \longrightarrow 2H_2O + N \vdots C \cdot C \vdots N \longleftarrow HON \vdots CH \cdot CH \vdots NOH$$
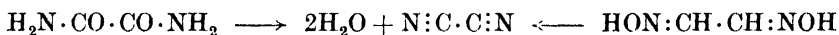
These reactions show that the two carbon atoms are linked together and exclude the alternative formulae $CN \cdot NC$ and $NC \cdot NC$. From stereochemical considerations, therefore, all the four atoms of the molecule must lie in a straight line, and this conclusion is confirmed by measurements of electron diffraction by the gas.[3] By this method the distances between the atoms can be obtained: that between carbon and nitrogen is $1 \cdot 16$ A and that between the two carbon atoms is $1 \cdot 43$ A; the latter distance is somewhat short for a typical single bond which is $1 \cdot 54$ A. As would be expected the molecule resembles diacetylene, $HC \equiv C - C \equiv CH$, in its electron diffraction. The symmetry of the molecule is shown by the fact that its electric moment is indistinguishable from zero.[4]

Cyanogen is a colourless gas of peculiar smell (boiling-point $-21 \cdot 35°$; melting-point $-27 \cdot 92°$). It is extremely poisonous and its effect on mammals is identical with that of prussic acid.[5] On heating to temperatures above $1000°$ it decomposes, the final products being carbon and nitrogen: in the temperature range $1124-1229°$ the free cyanogen radical has been detected by means of its band spectrum.[6] One volume of water will dissolve four volumes of cyanogen; the solution decomposes on standing and deposits a brown amorphous mass known as azulmic acid, while the solution contains ammonium oxalate, ammonium carbonate, hydrocyanic acid, and urea.

Cyanogen is the nitrile of oxalic acid and is hydrolysed to oxamide by concentrated hydrochloric acid or by hydrogen peroxide and alkali (see

[1] *Naturwiss.* 1931, **19**, 402.
[2] R. J. Strutt, *Proc. Roy. Soc.* 1911, A, **85**, 228.
[3] L. O. Brockway, *Proc. Nat. Acad. Sci.* 1933, **19**, 868.
[4] H. Braune and Th. Asche, *Z. phys. Chem.* 1931, B, **14**, 18.
[5] J. L. Burckhardt, *Zent.* 1913, ii. 606.
[6] G. B. Kistiakowsky and H. Gershinowitz, *J. chem. Phys.* 1933, **1**, 432.

p. 139); similarly with hydrogen sulphide it gives dithio-oxamide. It can be reduced by tin and hydrochloric acid to ethylene diamine,

$$H_2N \cdot CH_2 \cdot CH_2 \cdot NH_2.$$
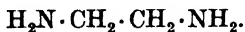
It resembles the halogens in reacting with dilute aqueous potash to give a mixture of cyanide and cyanate:

$$(CN)_2 + 2KOH \longrightarrow KCN + KOCN + H_2O.$$
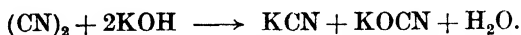
It is unable, however, to replace hydrogen attached to carbon by CN, even in a compound like phenol which can be chlorinated and brominated so readily.[1] Cyanogen reacts with polyhydric phenols in dry ether in the presence of hydrogen chloride in two ways, both of which are similar to the Houben-Hoesch reaction of nitriles (see p. 314): the products are hydrolysed on pouring into water.
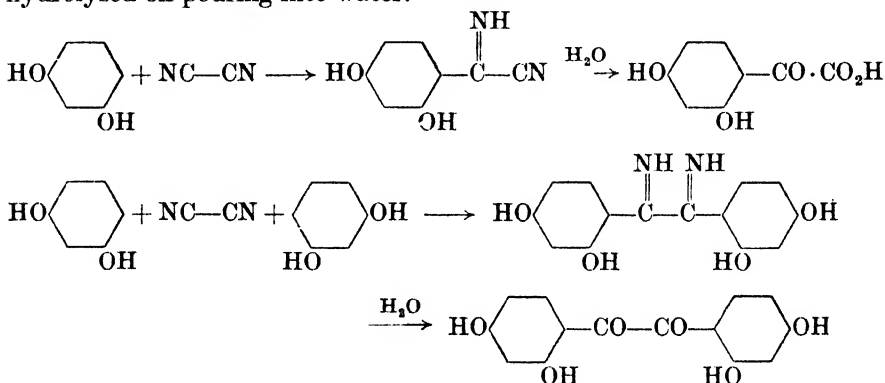
Unlike many of its derivatives, cyanogen does not polymerize to a triple polymer of ring structure: cyanuric cyanide (I), which might be expected,
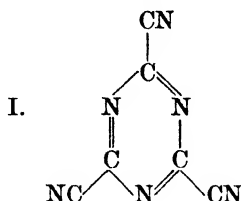
is formed by the action of phosphorus pentoxide on cyanuric amide[2] and breaks up quantitatively into cyanogen when passed as vapour over a red-hot platinum wire. Cyanogen polymerizes to an amorphous brown powder at temperatures in the region of 300°, and also when exposed to ultra-violet light.[3] The polymer is called paracyanogen and is formed quantitatively when an aqueous solution of potassium cyanide is electro-lysed. Its molecular weight is unknown, but is undoubtedly high: it is

[1] G. Machek, *Monats.* 1932, **61**, 87; 1933, **62**, 195.
[2] E. Ott, *Ber.* 1919, **52**, 656.
[3] T. R. Hogness and Liu-Sheng Ts'ai, *J. Amer. C. S.* 1932, **54**, 123.

reconverted into cyanogen at 800°. It is possible that it may contain a series of condensed six-membered rings.
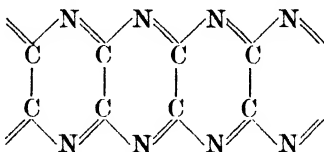
Thiocyanogen, $(SCN)_2$

Attempts to prepare this compound, which bears the same relation to the thiocyanates as cyanogen does to the cyanides, were made at an early date by J. von Liebig[1] and others, but only indefinite compounds of high molecular weight were obtained.

Thiocyanogen, which in German is called Rhodan, was first made by E. Söderbäck[2] by treating a metallic thiocyanate with a halogen in an inert solvent: the best method is to treat lead thiocyanate with a solution of bromine in dry ether at 0°: removal of the ether leaves the thiocyanogen. It can also be made by electrolysing a methyl-alcoholic solution of an alkali thiocyanate,[3] and by oxidizing thiocyanic acid in chloroform solution with lead tetracetate.[4] Thiocyanogen forms almost colourless crystals which melt at −3°. It is unstable and when warmed to ordinary temperatures becomes dark and viscous: eventually it turns to a red or orange solid which probably consists largely of a polymer $(SCN)_x$. These indeterminate polymers of thiocyanogen are also formed by electrolysing aqueous solutions of thiocyanates and by exposing such solutions to ultra-violet light in the presence of oxygen.[5] Thiocyanogen is decomposed rapidly by water forming thiocyanic, sulphuric, and prussic acids: it is for this reason that many of the earlier attempts to obtain it failed.

Like cyanogen, thiocyanogen resembles the halogens in some of its reactions, but to an even greater extent. It attacks a great many metals, including gold, with formation of thiocyanates: it can react with easily substituted benzene derivatives such as aniline, a thiocyanate residue entering the nucleus and thiocyanic acid being formed:

$$\phi \cdot NH_2 + (SCN)_2 \longrightarrow H_2N \cdot C_6H_4 \cdot SCN + HSCN.$$

Its molecular weight has been shown to correspond with the formula $(SCN)_2$ by an ingenious method.[6] If lead thiocyanate is added to a solution of bromine in a solvent of suitable freezing-point (bromoform was used), the freezing-point will not change if the thiocyanogen is $(SCN)_2$,

[1] *Pogg. Ann.* 1829, **15**, 548.
[2] *Annalen*, 1919, **419**, 217.
[3] H. Kerstein and R. Hoffmann, *Ber.* 1924, **57**, 491.
[4] H. P. Kaufmann and F. Kögler, ibid. 1925, **58**, 1553.
[5] S. S. Bhatnagar, H. B. Dunnicliff, and M. Ali, *J. Ind. C. S.* 1927, **4**, 229.
[6] H. Lecher and A. Goebel, *Ber.* 1921, **54**, 2223.

because the lead bromide formed is insoluble and the number of molecules in the solution remains the same:

$$Pb(SCN)_2 + Br_2 \longrightarrow PbBr_2 + (SCN)_2.$$
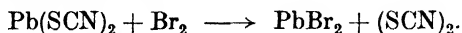
From its relation with the organic thiocyanates, thiocyanogen most probably has the structure $NC \cdot S \cdot S \cdot CN$, the two radicals being linked through the sulphur atoms.

If a benzene solution of thiocyanogen is shaken with ice-cold strong hydrochloric acid, the so-called dihydrochloride is formed: this is a crystalline compound which Söderbäck[1] has shown to be dichloriminodithiazolidine (I). Hydrogen chloride in dry ether, on the other hand, gives

I.   II.   III.
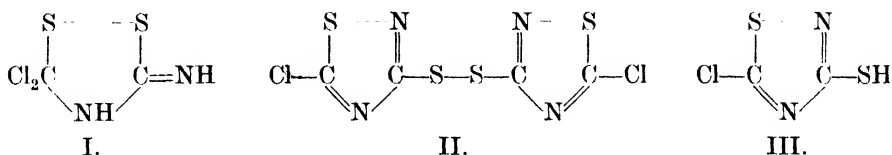
with thiocyanogen a compound free from hydrogen of formula $(SCN)_4Cl_2$:

$$3(SCN)_2 + 2HCl \longrightarrow (SCN)_4Cl_2 + 2HSCN.$$
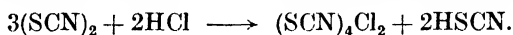
This compound has been shown by Söderbäck[2] to have the constitution (II), and probably results from the oxidation of a primary product (III) by thiocyanogen. A sodium salt of (III) can be obtained from (II): this salt reacts with aqueous sodium sulphide to give the sodium salt of the so-called perthiocyanic acid (IV).

IV.   V.
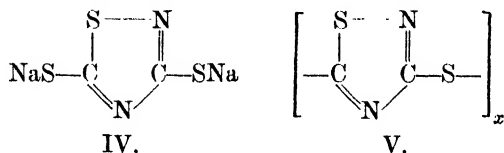
The sodium salt of (III) on standing breaks up into sodium chloride and another white form of polymerized thiocyanogen: this is most probably a long-chain polymer consisting of mercapto-thiodiazole units (V).

Thiocyanogen can be used as a substitution-reagent without isolation: if a compound such as aniline or α-naphthol is dissolved in cooled acetic acid together with sodium thiocyanate and bromine added, there is no bromination, but thiocyanogen is set free and thiocyano-substituted products are formed. Under the same conditions ethylene and stilbene add on thiocyanogen radicals at the double bond.[3]

The selenium analogue of thiocyanogen has been isolated as a crystalline solid by electrolysis of a solution of potassium selenocyanate in methyl alcohol.[4] Electrolysis of potassium cyanate, however, does not seem to give oxycyanogen but percyanic acid. Oxycyanogen appears to be a much

[1] loc. cit.   [2] *Annalen*, 1928, **465**, 184.
[3] H. P. Kaufmann and W. Oehring, *Ber.* 1926, **59**, 187.
[4] L. Birckenbach and K. Kellermann, ibid. 1925, **58**, 787.

less stable compound than thiocyanogen and probably reacts with water and alcohols; solutions containing it have been obtained by the action of iodine on silver cyanate in carbon bisulphide and carbon tetrachloride.[1]

Hydrocyanic Acid

The simplest derivative of cyanogen is hydrocyanic or prussic acid. It gives rise to derivatives of both the cyanide RCN and isocyanide RNC type, and it will be convenient to defer the discussion of the constitution of the acid itself until the properties of these derivatives have been described.

Hydrocyanic acid occurs in many plants combined as the glucosides of the cyanhydrins of various aldehydes and ketones. The best known of these is amygdalin, found in bitter almonds, which is hydrolysed by the enzyme emulsin present in the almonds to prussic acid, benzaldehyde, and two molecules of glucose. It has been stated that free prussic acid is found in certain plants, but this is untrue. The intact plant contains no free prussic acid, but as soon as it is damaged the protecting sugar group is hydrolysed by the plant enzymes giving the cyanhydrin which readily yields free prussic acid.

Prussic acid was discovered by C. W. Scheele in 1782 and first obtained as an anhydrous liquid by Gay-Lussac in 1811. It is formed whenever compounds containing carbon, hydrogen, and nitrogen or the elements themselves are heated to a high temperature; for example, when nitrogen and a hydrocarbon are passed through an arc,[2] or when ammonia comes into contact with red-hot coke. It is thus found in coal-gas and also in small amount in tobacco smoke.[3] It is produced by the action of active nitrogen on the vapours of various hydrocarbons,[4] and when many organic compounds, such as alcohols and sugars, are oxidized with nitric acid.

Simple methods of formation are the dehydration of formamide, best by passing the vapour over heated pumice or thoria, and the interaction of chloroform, ammonia, and alcoholic potash:

$$H \cdot CO \cdot NH_2 \longrightarrow HCN + H_2O$$

$$CHCl_3 + NH_3 + 3KOH \longrightarrow HNC + 3KCl + 3H_2O.$$
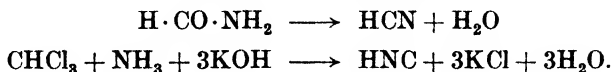
The first of these methods has been cited as evidence for the nitrile formula HCN, and the second for the isocyanide formula HNC: both are equally weak arguments. The most convenient method of preparing anhydrous prussic acid in the laboratory is by the interaction of aqueous solutions of sodium cyanide and sulphuric acid.[5] The yield is improved by the addition of a small amount of ferrous sulphate.[6]

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[1] H. Hunt, *J. Amer. C. S.* 1932, **54**, 907.

[2] A. Koenig and W. Hubbuch, *Z. Elektrochem.* 1922, **28**, 202.

[3] K. B. Lehmann and K. Gundermann, *Zent.* 1913, i. 456.

[4] R. J. Strutt, *Proc. Roy. Soc.* 1913, A, **88**, 544: 1915, **91**, 317.

[5] *Organic Syntheses*, Collective vol. 1, p. 307.

[6] K. H. Slotta, *Ber.* 1934, **67**, 1030.

The acid is a colourless liquid boiling at 25·7° and melting at −13·3°; it burns with a violet flame and has a smell like that of bitter almonds: people are said to differ more in their power of detecting this smell than any other. It is one of the most powerful poisons known: a dose fatal to man is of the order of 0·05 g.; its poisonous effect is mainly due to a total inhibition of all tissue respiration caused by its combination with the iron present in the respiration catalysts.[1] In cases of prussic acid poisoning there is usually little opportunity to administer antidotes because of the rapidity of its action. As antidotes oxidizing agents such as hydrogen peroxide have been used, but compounds which contain loosely bound sulphur are more efficient: they convert the acid into thiocyanic acid. Injection of sodium thiosulphate will protect an animal to some extent against prussic acid poisoning, but it removes the acid too slowly to act as an efficient antidote. The most satisfactory treatment seems to be to delay the physiological action of the prussic acid by injection of glucose or, better, dihydroxy-acetone, and remove it by injection of colloidal sulphur: rats which had been given nine times the fatal dose of prussic acid have recovered completely after this treatment.[2]

It seems strange that Scheele survived his discovery of the compound: he described its odour and taste but had no knowledge of its physiological action. L. Gattermann[3] recommends that any one working with the acid should smoke throughout the operations, because traces of the vapour which cannot be smelt can be detected by means of a characteristic and unpleasant flavour which they give to the tobacco; the same kind of thing happens with traces of phosgene, but the unpleasant flavours are quite distinct. Liquid prussic acid is manufactured on an industrial scale and is used for the destruction of pests, such as rats in ships and noxious insects in orchards:[4] for such purposes it is sometimes mixed with lachrymatory substances so that its presence will be more obvious. The salts of prussic acid are all as poisonous as the free acid and their action on the body is identical with that of the acid. This is largely due to the fact that in the stomach they are decomposed by the free hydrochloric acid there to give prussic acid. It is well known that the first attempts to assassinate Rasputin in Petrograd in 1916 were by poisoning his wine with potassium cyanide and that he swallowed much more than a fatal dose without any effect. This is said to be because he suffered from alcoholic gastritis, a condition when there is no free acid in the stomach.[5] The action of the poison, most probably, was further delayed because he was inordinately fond of sweetmeats and his system must have contained much glucose.

Hydrocyanic acid has a dielectric constant of 194·4 at −13·4°, which is

[1] O. Warburg, *Ber.* 1925, **58**, 1001.

[2] A. W. Forst, *Arch. exp. Path. und Pharm.* 1928, **128**, 1.

[3] *Annalen*, 1907, **357**, 319.

[4] An interesting account of the manufacturing process by P. J. Carlisle will be found in *Ind. Eng. Chem.* 1933, **25**, 959, and a monograph by G. Peters, *Ahrens' Sammlung*, 1930, vol. **20**, deals with the uses of prussic acid.

[5] E. Leschke, *Clinical Toxicology*, 1934, p. 145.

the highest that has been measured, but it is on the whole a poor solvent for salts, and acids such as sulphuric and trichloracetic acids give solutions whose conductivities are much smaller than those in water, in spite of the fact that the viscosity of liquid prussic acid is only about one-fifth that of water.[1] The acid when pure is a stable substance: if it contains traces of impurities, especially if they are alkaline, it turns yellow and then deposits an amorphous dark brown compound usually called azulmic acid, although that term is sometimes applied to an indefinite compound derived from cyanogen (see p. 301). The acid can be stabilized by adding a trace of mineral acid to neutralize the alkali from the glass.[2] In aqueous solution the decomposition is accelerated by alkali and by light: a brown precipitate of azulmic acid forms and ammonia, formic acid and other compounds remain in solution. A polymerized form of prussic acid can be extracted from the aqueous solution after standing, and this is hydrolysed by acids or alkalis to ammonia, carbon dioxide, and glycine: it is probably the dinitrile of amino-malonic acid.

$$3HCN \longrightarrow H-\underset{\underset{CN}{|}}{\overset{\overset{CN}{|}}{C}}-NH_2 \longrightarrow \underset{\underset{CO_2H}{|}}{\overset{\overset{CO_2H}{|}}{C}}H \cdot NH_2 \longrightarrow CO_2 + CH_2(NH_2) \cdot CO_2H$$
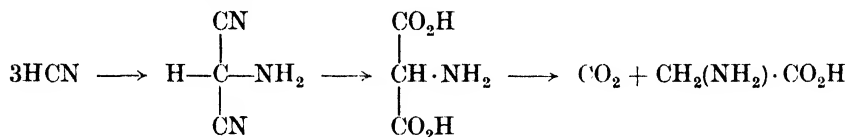
Prussic acid can be reduced to methylamine by zinc and hydrochloric acid or catalytically by hydrogen and colloidal palladium. The reaction can be used for the commercial preparation of methylamine by passing prussic acid and hydrogen over certain metallic cyanides which act as catalysts at 200–300°. The acid behaves as the nitrile of formic acid: it can be hydrolysed to formic acid, best by heating its sodium salt with water to 190° under pressure.[3] The rate of hydrolysis by mineral acids has been measured by V. N. Kreible and A. L. Peiker:[4] with hydrochloric and hydrobromic acids it increases extremely rapidly with the concentration of the acid and also on addition of salts of the acids such as sodium chloride. The hydrolysis seems to be due mainly to the undissociated molecules of these acids. Sulphuric acid is much less efficient in bringing about hydrolysis.

Prussic acid reacts with diazomethane to give mainly methyl cyanide (acetonitrile). This was at one time considered strong evidence for the nitrile formula for the acid. A. Peratoner and F. C. Palazzo,[5] however, have shown that methyl isocyanide is formed at the same time, and in any case such evidence is of little value.

Prussic acid forms a large number of addition compounds, some of which lead to important synthetical methods. With hydrogen chloride in dry ethyl acetate it gives a compound 2HCN,3HCl which is dichlor-

[1] K. Fredenhagen and J. Dahmlos, *Z. anorg. Chem.* 1929, **179**, 77.

[2] W. Lewcock, *Pharm. J.* 1918, **47**, 50.

[3] H. Sulzer, *Z. angew. Chem.* 1912, **25**, 1268.

[4] *J. Amer. C. S.* 1933, **55**, 2326.   [5] *Atti R.* 1907, [V], **16**, ii, 432, 501.

methyl-formamidine hydrochloride (I);[1] this is shown by the facts that it is hydrolysed by alcohol to formamidine and reacts with benzene in the presence of aluminium chloride to give diphenylmethyl-formamidine (II).

$$\text{I. HC}\begin{array}{l}\diagup\text{NH}_2 \text{ [Cl]}\\ \diagdown\text{NH} \cdot \text{CHCl}_2\end{array} \qquad \text{II. HC}\begin{array}{l}\diagup\text{NH}\\ \diagdown\text{NH} \cdot \text{CHPh}_2\end{array}$$

$$\text{HC}\begin{array}{l}\diagup\text{NH}\\ \diagdown\text{NH} \cdot \text{CHCl}_2\end{array} + 2\text{EtOH} \longrightarrow 2\text{EtCl} + \text{H} \cdot \text{CO}_2\text{H} + \text{HC}\begin{array}{l}\diagup\text{NH}\\ \diagdown\text{NH}_2\end{array}.$$
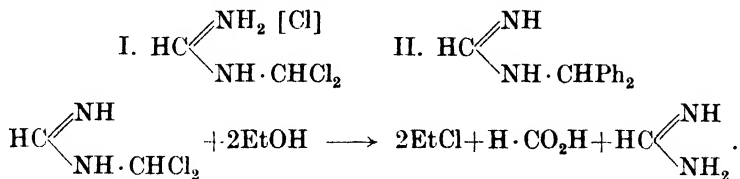
Hydrogen chloride and prussic acid form another compound which is most conveniently obtained by heating the above compound, when hydrogen chloride is lost and a second volatile compound distils.[2] This compound is chloromethylene-formamidine, $HN:CH \cdot N:CHCl$. Finally a compound containing equimolecular proportions of hydrogen chloride and prussic acid, formimino-chloride, $HN:CHCl$, has been postulated but has never been isolated.

The interest which attaches to these compounds arises from the question of the mechanism of Gattermann's synthesis of aromatic aldehydes. This reaction is of the Friedel-Crafts type and consists in the interaction of an aromatic compound with hydrogen chloride and hydrogen cyanide to give a product which is readily hydrolysed to an aldehyde; it can be represented as follows:

$$\text{ArH} + \text{HCN} + \text{HCl} \longrightarrow \text{ArCH:NH,HCl} \longrightarrow \text{ArCHO}.$$

The mechanism of the reaction is, however, more complicated than this equation suggests. The ease with which the reaction takes place varies according to the nature of the aromatic compound. Polyhydric phenols with the hydroxyl groups in the meta position to one another, such as resorcinol and phloroglucinol, react very readily in ether, benzene and other anhydrous solvents, and no aluminium chloride need be added; to obtain good yields of the aldehyde, however, the hydrogen cyanide must be in excess. Other phenols and phenolic ethers will react in ether only if zinc chloride is present, while for others aluminium chloride must be used. In all these cases the reaction takes place below 40°; at temperatures above 50° the aromatic hydrocarbons themselves are attacked in the presence of aluminium chloride, and at 100° toluene can be converted quantitatively into p-tolualdehyde.

For long it has been supposed that the reaction involved the addition of one molecule of hydrogen chloride to one of hydrogen cyanide to give formimino-chloride which then by a Friedel-Crafts reaction gave the aldimine. The hydrochloride of the latter does, in fact, separate during the reaction with polyhydric phenols:

$$\text{ArH} + \text{ClCH:NH} \longrightarrow \text{ArCH:NH,HCl}.$$
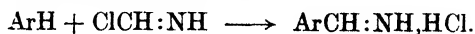
This scheme does not explain why the hydrogen cyanide must be in excess,

[1] L. Gattermann and K. Schnitzspahn, *Ber.* 1898, **31**, 1770.

[2] L. E. Hinkel and R. T. Dunn, *J.C.S.* 1930, 1834.

and since with equimolecular proportions of the reagents the yield of aldehyde never exceeds 50 per cent. of that calculated from the amount of hydrogen cyanide used, it was suggested that the actual reactant is chloromethylene-formamidine, and not formimino-chloride, and that the reaction should be written:[1]

$$\text{ArH} + \text{ClCH:N·CH:NH} \longrightarrow \text{ArCH:N·CH:NH,HCl}$$
$$\longrightarrow \text{ArCHO} + 2\text{NH}_4\text{Cl} + \text{HCO}_2\text{H}.$$
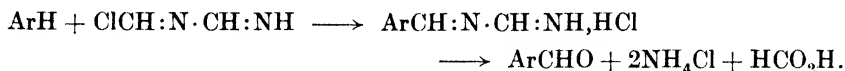
This reaction has been shown to take place with resorcinol; the hydrochloride of the intermediate product, resorcylmethylene-formamidine, separates from the reaction mixture in quantitative yield, and can be hydrolysed to resorcylaldehyde. The reaction of polyhydric phenols with hydrogen cyanide and hydrogen chloride cannot, however, follow this course, because the intermediate product obtained is the aldimine hydrochloride and not a substituted methylene-formamidine, and the latter is not converted into the former under the conditions of the reaction.[2] Hence the question of the mechanism of the reaction with phenols remains obscure.

When aluminium chloride must be present for the reaction to take place, the mechanism is undoubtedly different.[3] Aluminium chloride and hydrogen cyanide form a compound, $\text{AlCl}_3,2\text{HCN}$, which unites with hydrogen chloride to form a compound, $\text{AlCl}_3,2\text{HCN},\text{HCl}$, identical with that obtained by the direct union of aluminium chloride and chloromethylene-formamidine. This latter compound dissociates on heating, and the actual reaction takes place between the chloromethylene-formamidine and the aromatic compound under the influence of the free aluminium chloride in a normal Friedel-Crafts manner. The actual reactant is definitely not formimino-chloride. Only very rarely can more than one aldehyde group be introduced into a molecule by the Gattermann reaction.

A convenient modification of the Gattermann aldehyde synthesis which avoids the use of free prussic acid is due to R. Adams and I. Levine.[4] Anhydrous zinc cyanide is added to a solution of the phenol in benzene or ether and dry hydrogen chloride passed in: in this way the anhydrous zinc chloride and prussic acid necessary for the reaction are formed *in situ*. This modification can also be used in the cases where aluminium chloride is necessary. Dry potassium or sodium cyanides cannot be used in place of the zinc salt.

Hydrocyanic acid is able to add on to the double bond of certain types of unsaturated compounds. The best known example of this reaction is

[1] L. E. Hinkel, E. E. Ayling, and W. H. Morgan, *J.C.S.* 1932, 2793.

[2] L. E. Hinkel, E. E. Ayling, and J. H. Benyon, ibid. 1936, 184.

[3] L. E. Hinkel and R. T. Dunn, ibid. 1931, 3343; L. E. Hinkel, E. E. Ayling, and J. H. Benyon, ibid. 1935, 674; 1936, 184.

[4] *J. Amer. C. S.* 1923, **45**, 2373: see also R. Adams and E. Montgomery, ibid. 1924, **46**, 1518.

with the carbonyl group: aldehydes and ketones in most cases can add on hydrocyanic acid to form a cyanhydrin:

$$>C{:}O + HCN \longrightarrow >C(OH){\cdot}CN.$$
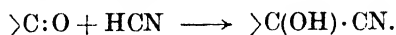
The reaction is, in mechanism, not strictly one of hydrocyanic acid, since, as A. Lapworth has shown,[1] there is little or no addition in the presence of mineral acids when all the prussic acid is in the undissociated form. On the other hand, bases act as powerful catalysts. The results can be very readily demonstrated in the case of camphor quinone, where the reaction can be followed colorimetrically, the quinone being yellow and its cyanhydrin colourless. With the equivalent of hydrogen cyanide a solution of camphorquinone is decolorized in 8–10 hours, showing that cyanhydrin formation is complete. If a trace of mineral acid is added there is no loss of colour in 14 days, while with one drop of 15 per cent. aqueous caustic potash, the colour disappears in a few seconds. The actual reactant is the cyanide ion which forms with the aldehyde or ketone the ion of the cyanhydrin: this later unites with a proton to give the cyanhydrin itself:

$$>C{:}O + CN^- \longrightarrow >C(CN){\cdot}O^- \xrightarrow{H^+} >C(CN){\cdot}OH.$$
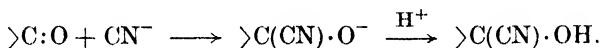
With benzaldehyde and certain other aldehydes the potassium salt of the cyanhydrin can be isolated at low temperatures from a mixture of the aldehyde and aqueous potassium cyanide.[2] The reaction is reversible and is incomplete even with aldehydes:[3] the position of equilibrium varies with the nature of the aldehyde or ketone, and in the case of the substituted benzaldehydes with the nature of the substituent.[4] A convenient method for preparing many cyanhydrins, which serve as intermediates in the preparation of α-hydroxyacids and other compounds, is the interaction of aqueous sodium cyanide and the bisulphite compound of the aldehyde or ketone. This is especially useful with aromatic aldehydes, because the other reaction which can take place between the aldehyde and an alkali cyanide, benzoin formation, is repressed under these conditions. Benzoin formation involves the interaction of the ion of the cyanhydrin with a molecule of aldehyde to give the hydroxyketone:[5]

$$\phi{\cdot}CH(CN)O^- + \phi{\cdot}CHO \longrightarrow \phi{\cdot}CH(OH){\cdot}CO{\cdot}\phi + CN^-.$$
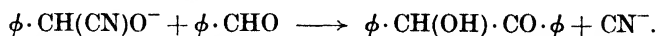
Another useful method of preparing cyanhydrins in cases where benzoins are apt to be formed is to shake a solution of the aldehyde in ether or ligroin with an aqueous solution of potassium cyanide and its equivalent of ammonium chloride. Under these conditions neither the amino-nitrile (see p. 117) nor the benzoin is formed, but the cyanhydrin separates in good yield.[6]

Products in which prussic acid has been added to the double bond

[1] *J.C.S.* 1903, **83**, 995.   [2] A. Lapworth, ibid. 1904, **85**, 1206.
[3] W. J. Jones, ibid. 1914, **105**, 1560.
[4] A. Lapworth and R. H. F. Manske, ibid. 1928, 2533.
[5] A. Lapworth, ibid. 1903, **83**, 1004.   [6] A. Albert, *Ber.* 1916, **49**, 1382.

$>$C=N— can also be obtained. Thus the bisulphite compound of a Schiff's base reacts with potassium cyanide:

$$RN:CHR' \longrightarrow RNH \cdot CHR' \cdot SO_3Na \longrightarrow RNH \cdot CHR' \cdot CN.$$
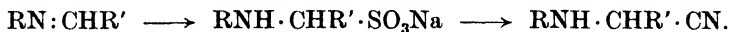
With the double bond between carbon atoms addition only takes place when a group such as a keto, nitrile, or carboxyl group is conjugated with the double bond. Thus from benzylidene benzyl cyanide, the dinitrile of diphenylsuccinic acid is obtained:[1]

$$\phi CH:C\phi \cdot CN + HCN \longrightarrow \phi CH(CN) \cdot CH\phi(CN).$$
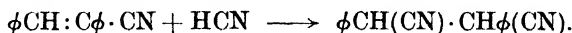
Such reactions are catalysed by basic substances and it seems that, as with the carbonyl compound, the actual reactant is the cyanide ion.[2] The mechanism of addition to an unsaturated ketone is most probably

$$\cdot CH:CH \cdot CO \cdot \longrightarrow \cdot CH(CN) \cdot CH:C \overset{H^+}{\underset{O^-}{\longrightarrow}} \cdot CH(CN) \cdot CH_2 \cdot CO \cdot$$
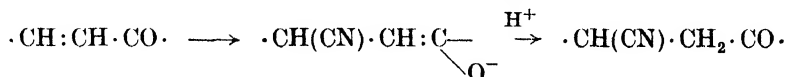
In practice the $\alpha\beta$-unsaturated compound is often treated in alcoholic solution with aqueous sodium cyanide, when the addition compound separates as its sodium salt; the latter is then decomposed with dilute acid.[3]

A similar reaction takes place with activated triple bonds; the formation of amino-malonic nitrile by polymerization of prussic acid is an example where two molecules of the acid add on to the triple bond of a third.

Nitriles

The nitriles are the derivatives of hydrocyanic acid in which the substituting group is attached to carbon: they have the general formula $RC:N$. They can be hydrolysed to acids and hence are often regarded not as derivatives of prussic acid but of the acids which they yield on hydrolysis. Accordingly $CH_3 \cdot CN$, for example, can be called methyl cyanide but is more frequently called acetonitrile, since it can be converted into acetic acid.

The first nitrile to be prepared was propionitrile, which J. Pelouze obtained in 1834 by distilling barium ethyl sulphate with potassium cyanide. H. Kolbe showed later that on hydrolysis they yield acids containing the same number of carbon atoms, a reaction which establishes their constitution.

Nitriles can be obtained by many methods of which only the more important will be described. They can be divided into two classes. In the first the carbon chain is lengthened.

(i) They are formed by the interaction of a metallic cyanide, usually

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[1] A. Lapworth, loc. cit.   [2] Cf. E. Knoevenagel, *Ber.* 1904, **37**, 4065.
[3] L. Higginbotham and A. Lapworth, *J.C.S.* 1922, **121**, 49; W. Baker and A. Lapworth, ibid. 1925, **127**, 560.

potassium cyanide, with an organic halide. Thus benzyl chloride and potassium cyanide give benzyl cyanide:

$$\phi \cdot CH_2 \cdot Cl + KCN \longrightarrow \phi \cdot CH_2 \cdot CN + KCl.$$
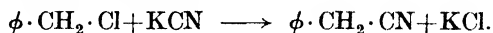
This is one of the most important methods of preparation, not so much because good yields are obtained as because of the ease of getting the starting materials. The reaction does not take place, or only with difficulty, with compounds which contain a non-reactive halogen atom such as chlorobenzene. A solvent is needed and is usually alcohol: the reaction is often slow and in some cases the reaction mixture must be boiled for two or three days. The halide can be replaced by a salt of an alkyl sulphuric acid as in Pelouze's preparation: in this case the two salts are mixed and distilled.

$$KCN + KO \cdot SO_2 \cdot OEt \longrightarrow Et \cdot CN + K_2SO_4$$
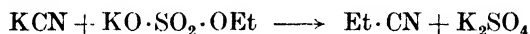
In both these reactions a little isocyanide is often formed: this can be removed by shaking with cold hydrochloric acid which immediately destroys the isocyanide and hardly affects the nitrile.

(ii) In the aromatic series a rather similar method is to distil a mixture of potassium cyanide (or ferrocyanide) and a salt of a sulphonic acid: potassium sulphite remains.

$$\phi \cdot SO_2 \cdot OK + KCN \longrightarrow \phi \cdot CN + K_2SO_3$$
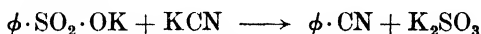
(iii) Grignard compounds react with cyanogen chloride to give the nitrile:

$$R \cdot MgCl + Cl \cdot CN \longrightarrow RCN + MgCl_2.$$
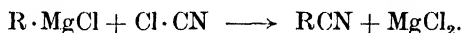
The reaction is carried out by passing a stream of the gaseous cyanogen chloride into the ethereal solution of the organo-magnesium compound, and in many cases the yields are good. The bromide or iodide of cyanogen cannot be used because the reaction takes another course and leads to the bromo- or iodo-compound.[1] Cyanogen can be used instead of its chloride. If two molecules of the Grignard compound are used, the nitrile formed is, of course, attacked by the excess of the Grignard compound and an imine results (see p. 313).

(iv) An isocyanide undergoes rearrangement to a cyanide on heating to 100–200°.

(v) Cyanogen chloride or bromide will condense with aromatic hydrocarbons in the presence of anhydrous aluminium chloride. Good yields are obtained in this Friedel-Crafts reaction, if the reactants are pure.[2]

(vi) Aromatic nitriles can often be obtained easily by pouring a solution of a diazonium salt into one of cuprous cyanide in potassium cyanide (Sandmeyer reaction, see p. 407): $Ar \cdot N_2Cl \longrightarrow Ar \cdot CN + N_2$. Nickel cyanide often gives better yields than cuprous cyanide.[3]

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[1] V. Grignard and C. Courtot, *Bull. Soc. chim.* 1915, [iv], **17**, 228.

[2] P. Karrer and E. Zeller, *Helv. Chim. Acta*, 1919, **2**, 482; P. Karrer, A. Rebmann, and E. Zeller, ibid. 1920, **3**, 261.

[3] A. Korczynski, W. Mrozinski, and W. Vielau, *C.r.* 1920, **171**, 182; Korczynski and B. Fandrich, ibid. 1926, **183**, 421.

The second class of reactions is that in which the number of carbon atoms in the molecule remains the same.

(vii) The most obvious example is the dehydration of an amide: $R \cdot CONH_2 \longrightarrow RCN$ (see p. 145). This is best carried out by warming with thionyl chloride; distillation with phosphorus pentoxide can be used, but the yields are not so good.

(viii) An acid can often be converted directly into the nitrile by distilling with a thiocyanate. It is best to use the zinc salt of the acid and lead or cuprous thiocyanate.[1] The method gives good yields with many aromatic acids, but cannot be used with amino-, nitro-, or hydroxy-acids: in the main it takes place according to the equation:

$$(R \cdot CO_2)_2 Zn + Pb(SCN)_2 \longrightarrow 2RCN + PbS + ZnS + 2CO_2.$$
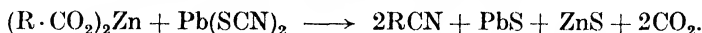
Other reactions in which nitriles are formed include cyanhydrin formation (see p. 309), Strecker's reaction (p. 117), and the dehydration of aldoximes (p. 173). They are also formed to some extent in the action of bromine and caustic potash on an amide: the normal product is the amine (see p. 18), but if the acid contains a carbon chain of more than about five atoms, there is a tendency for the hypobromite to convert the amine into the dibromo compound which loses hydrogen bromide to give the nitrile.

$$RCH_2 \cdot CO \cdot NH_2 \longrightarrow RCH_2 \cdot NH_2 \longrightarrow RCH_2 \cdot NBr_2 \longrightarrow RCN$$

Properties of the Nitriles

The lower nitriles are liquids which distil without decomposition: the higher members are crystalline solids.

	m.p.	b.p.
Acetonitrile	$-41°$	$81 \cdot 6°$
Propionitrile	..	$98°$
n-Butyronitrile	..	$118 \cdot 5°$
Stearonitrile	$+41°$	$274 \cdot 5°/100$ mm.
Benzonitrile	$-12°$	$191°$
Benzyl cyanide	$-24 \cdot 6°$	$233°$

With the exception of the lower members they are only slightly soluble in water. Their reactions with acids to form secondary amides, with anhydrides to form tertiary amides, with hydroxylamine to give amidoximes and with alcohols to give imino-ethers are referred to elsewhere.

They are hydrolysed both by acids and alkalis to a carboxylic acid and ammonia:

$$R \cdot CN \longrightarrow R \cdot CO_2 H + NH_3.$$
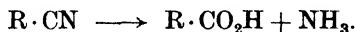
The amide is an intermediate stage in the hydrolysis, but cannot be isolated in the case of the simple aliphatic nitriles because as S. Kilpi has shown[2] the amides are much more rapidly hydrolysed by acids and alkalis than the nitriles. In some other cases, however, the amide is very resistant to hydrolysis, and is the sole product of the hydrolysis of the nitrile. The commonest way to hydrolyse a nitrile is to boil it with strong hydrochloric

[1] E. E. Reid, *Amer. Chem. J.* 1910, **43**, 162; G. D. van Epps and E. E. Reid, *J. Amer. C. S.* 1916, **38**, 2120.   [2] *Z. phys. Chem.* 1914, **86**, 641, 740.

acid or with aqueous sulphuric acid; if the reaction is slow because of the low solubility of the nitrile, the addition of glacial acetic acid often improves matters. Alkaline hydrolysis, usually with strong alcoholic potash, is also used, and some nitriles which resist the action of acids are hydrolysed under those conditions. For very resistant nitriles, particularly those where ortho-substituents hinder the reaction by their steric effect, the best reagent is orthophosphoric acid followed by addition of water.[1] Thus 2,6-dimethylbenzonitrile, in which both positions ortho to the CN group are filled, is not attacked by caustic potash in ethyl or amyl alcohol and only partly converted into the amide by sulphuric acid, and this cannot be hydrolysed further except by anhydrous orthophosphoric acid. The reaction clearly depends on compound formation with the phosphoric acid, because it fails with 92·5 per cent. phosphoric acid.

The conversion of a nitrile directly into an amide by alkaline hydrogen peroxide has been discussed above: if perhydrol (30 per cent. H_2O_2) is used, the hydrolysis often goes further and the acid is obtained.[2]

A nitrile can be reduced either to an imine, or to a primary amine:

$$R \cdot CN \longrightarrow R \cdot CH:NH \longrightarrow R \cdot CH_2 \cdot NH_2.$$

To obtain the imine, the conditions must be chosen with great care, and since these imines are very readily hydrolysed to aldehydes,

$$R \cdot CH:NH \longrightarrow R \cdot CHO + NH_3,$$
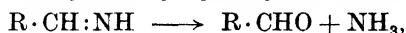
reduction of nitriles to this stage is a very convenient way of preparing certain aldehydes. A. Sonn and E. Müller[3] found that 'imino-chlorides' (see p. 153) can be reduced by anhydrous stannous chloride to imines: $R \cdot CCl:N\phi \longrightarrow R \cdot CH:N\phi$. This method has been modified so that the nitrile itself can be used and the preparation of the imino-chlorides avoided.[4] Anhydrous stannous chloride, which separates out when the hydrated salt, $SnCl_2,2H_2O$, is treated with acetic anhydride,[5] is suspended in dry ether and the mixture saturated with dry hydrogen chloride: two liquid layers form, the lower containing the stannous chloride. The nitrile is added with shaking, and in many cases the stannichloride of the aldimine, $(R \cdot CH:NH,HCl)_2SnCl_4$, begins to separate at once. In other cases the mixture must be heated for some time.[6] The salt is rapidly hydrolysed by warm water to give the aldehyde. More vigorous reduction leads to the amine. For this purpose sodium and either ethyl or amyl alcohol are used. The reaction (Mendius) has been discussed above (see p. 16).

With Grignard reagents nitriles react to give derivatives of ketimines, which are hydrolysed to ketones but not quite as readily as the aldimines.

$$R \cdot CN + R' \cdot MgHal \longrightarrow \underset{R'}{\overset{R}{\diagdown}}C{=}N \cdot MgHal \longrightarrow \underset{R'}{\overset{R}{\diagdown}}C{=}O$$
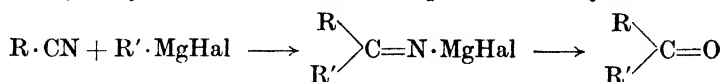
[1] G. Berger and S. C. J. Olivier, *Rec. trav. chim.* 1927, **46**, 600; S. C. J. Olivier, ibid. 1929, **48**, 568. [2] E. Oliveri-Mandalà, *Gazz.* 1922, **52**, [i] 107.
[3] *Ber.* 1919, **52**, 1927. [4] H. Stephen, *J.C.S.* 1925, **127**, 1874.
[5] Ibid. 1930, 2786. [6] F. E. King, P. L'Ecuyer, and H. T. Openshaw, ibid. 1936, 352.

This reaction is often useful for the synthesis of ketones,[1] and is of general application except in the case of the lower aliphatic nitriles which polymerize under the action of the Grignard compound, and of those nitriles in which a hydrogen atom is easily replaced by a metal, such as benzyl cyanide, $\phi \cdot CH_2 \cdot CN$, and cyanacetic ester, $NC \cdot CH_2 \cdot CO_2Et$. These latter behave like acids and decompose the organic magnesium compound. The reaction is usually carried out by adding the nitrile to the ethereal solution of the Grignard compound, heating for the requisite time and decomposing the ketimine derivative with aqueous ammonium chloride. The best yields are obtained from aromatic nitriles.[2]

Another useful method of obtaining ketones from nitriles is the Hoesch reaction,[3] which is similar to Gattermann's aldehyde synthesis with the difference that a nitrile replaces hydrogen cyanide. The reaction takes place readily with polyhydric phenols in which at least two hydroxyl groups are in the meta position to one another, and with the ethers of such phenols in which at least one hydroxy group is free. With the more reactive compounds the phenol and nitrile are mixed in dry ether and the solution saturated with dry hydrogen chloride. After standing in the cold an imine hydrochloride separates as a solid and on treatment with water gives a ketone. Thus acetonitrile and resorcinol give resacetophenone.

$$HO-\langle\!\bigcirc\!\rangle-OH + MeCN \longrightarrow HO-\langle\!\bigcirc\!\rangle\overset{\overset{NH,HCl}{\|}}{-C}\cdot Me \longrightarrow HO-\langle\!\bigcirc\!\rangle-CO\cdot Me$$
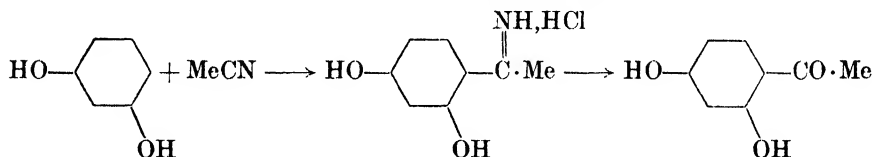
With the less reactive phenols zinc chloride must be added as well; in such cases the solid which separates is the double chloride of the imine with zinc chloride.

The reaction is often thought to proceed by way of the imino-chloride, $R \cdot CCl{:}NH$, which condenses with the phenol in a Friedel-Crafts manner. This view is perhaps questionable in view of the doubts concerning the existence of imino-chlorides, and complex formation in which the zinc chloride is involved is a possible factor in the mechanism of the reaction.[4]

Nitriles in which there is a hydrogen atom attached to the carbon atom which carries the cyanide group tend to behave as very weak acids; if there is also present some group such as phenyl, the salts with metals can be obtained if both moisture and oxygen are rigidly excluded. Thus benzyl cyanide forms a sodium or potassium salt when treated with the metal in some neutral solvent in an atmosphere of nitrogen.[5] The hydrogen

[1] E. E. Blaise, *C.r.* 1901, **132**, 839; **133**, 1217.

[2] L. Bary, *Bull. Soc. chim.* 1922, **31**, 397; E. Ectors, *Bull. Soc. chim. Belg.* 1924, **33**, 146. [3] K. Hoesch, *Ber.* 1915, **48**, 1122; 1917, **50**, 462.

[4] A list of references to the uses of the reaction is given by J. Houben and W. Fischer, *J. pr. Chem.* 1929, **123**, 89.

[5] F. W. Upson, R. T. Maxwell, and H. M. Parmelee, *J. Amer. C. S.* 1930, **52**, 1971; cf. M. M. Rising and E. W. Lowe, ibid. 2524.

displaced by the metal is not evolved, but reduces some of the nitrile to toluene, sodium cyanide being formed at the same time. The salts are spontaneously inflammable in air: their constitution must be written $\phi \cdot CH:C:N^-[Na]$, and they are derived from a tautomeric form of the nitrile, as is indicated by their reactions. When heated, the sodium salt gives sodium cyanide and stilbene which is formed by the union of two benzylidene radicals:

$$2[\phi \cdot CH:C:N]Na \longrightarrow 2NaCN + \phi \cdot CH:CH \cdot \phi.$$
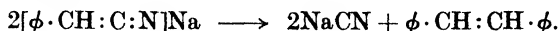
Oxidation with air leads to benzoic acid and sodium cyanide:

$$\phi \cdot CH:C:N[Na] \longrightarrow NaCN + \phi \cdot CO_2H.$$
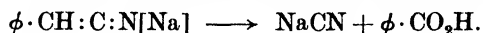
If treated with ethyl iodide, the ethyl group becomes attached to the carbon atom,

$$\phi \cdot CH:C:N[Na] \longrightarrow NaI + \phi \cdot CHEt \cdot CN,$$
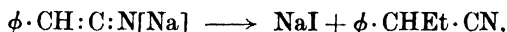
and this has led to the suggestion that the ion is tautomeric and consists of two forms in equilibrium, $[\phi \cdot CH:C:N^-] \rightleftharpoons [\phi \cdot \overline{C}H \cdot C:N]$. The ion is now, however, to be regarded as a hybrid which exhibits resonance: the reaction with ethyl iodide is exactly paralleled by its action with the sodium derivative of ethyl acetoacetate which gives a C-ethyl product and not an O-ethyl compound.

$$CH_3 \cdot \overset{\displaystyle O^- [Na]}{\underset{\displaystyle }{C}} = CH \cdot CO_2Et \longrightarrow NaI + CH_3 \cdot CO \cdot CHEt \cdot CO_2Et$$
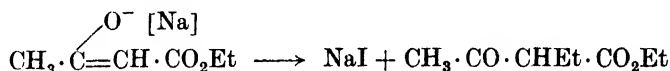
The reactivity and instability of the salts of these nitriles almost certainly arise from the strained state of the carbon atom, which is twice doubly bound and is thus comparable with a carbon atom in a ketene, $R_2C:C:O$. The sodium salt of α-cyano-esters, such as cyanacetic ester $CH_2(CN) \cdot CO_2Et$, is a much more stable substance: in this, however, it is the carbethoxy group and not the cyano group which is involved in the salt formation.[1]

The formation of salts by these nitriles is doubtless connected with certain additive reactions which such nitriles show in the presence of sodium or sometimes sodium ethoxide. An example is the condensation of benzyl cyanide with cinnamic ester to form a derivative of glutaric acid.[2]

$$\phi \cdot CH_2 \cdot CN + \phi \cdot CH:CH \cdot CO_2Et \longrightarrow \begin{matrix} \phi \cdot CH \cdot CH_2 \cdot CO_2Et \\ | \\ \phi \cdot CH \cdot CN \end{matrix}$$
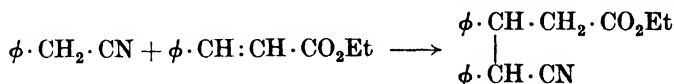
A commoner case is the so-called polymerization of nitriles to bimolecular substances. This is a simple addition to the treble bond of a second molecule of nitrile. If acetonitrile in ether is treated with metallic sodium, the sodium salt of the nitrile is first formed: it has never been isolated, but methane is evolved and sodium cyanide separates, and this is similar to the salt formation of benzyl cyanide:

$$2Na + 2CH_3CN \longrightarrow NaCN + CH_4 + CH_2:C:N[Na].$$

The salt then condenses with a further molecule of the nitrile to give the

[1] J. F. Thorpe, J.C.S. 1900, **77**, 923.   [2] S. Avery, J. Amer. C. S. 1928, **50**, 2512.

nitrile of imino-acetoacetic acid, whose constitution is shown by the fact that it is hydrolysed by dilute acid in the cold to a keto-nitrile, and on heating to acetoacetic acid which breaks up into acetone and carbon dioxide.

$$CH_3 \cdot C:N \quad \longrightarrow \quad CH_3 \cdot C:NH \quad \longrightarrow \quad CH_3 \cdot CO \quad \longrightarrow \quad CH_3 \cdot CO \cdot CH_3$$
$$+ \qquad\qquad | \qquad\qquad\qquad | \qquad\qquad\qquad +$$
$$CH_2:C:N[Na] \qquad CH_2 \cdot CN \qquad\quad CH_2 \cdot CN \qquad\quad CO_2$$
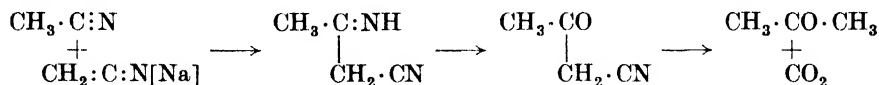
The same reaction is shown by benzyl cyanide, which will condense with itself or with purely aromatic nitriles such as o-toluic nitrile. The reaction has been studied in detail by J. F. Thorpe, and the products undergo a variety of interesting ring closures which cannot be discussed here.[1]
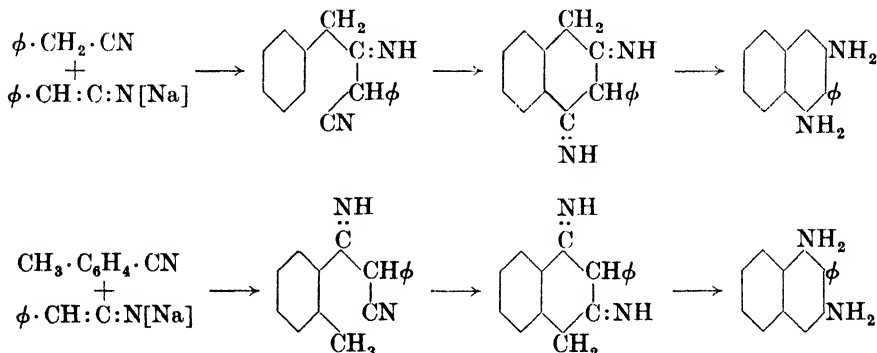
An interesting extension of this reaction is to the dinitriles of dibasic acids where, both cyano groups being in the same molecule, ring closure takes place. J. F. Thorpe[2] found that if adiponitrile is heated with a trace of sodium ethoxide in alcoholic solution, it is converted quantitatively into imino-cyano-cyclopentane: this is hydrolysed by dilute acids to 2-cyano-cyclopentanone and with stronger acids to the carboxylic acid which, being a β-ketonic acid, loses carbon dioxide to give cyclopentanone.

$$\begin{array}{c} CH_2 \cdot CH_2 \cdot CN \\ | \\ CH_2 \cdot CH_2 \cdot CN \end{array} \longrightarrow \begin{array}{c} CH_2 \cdot CH_2 \\ | \qquad\quad >C:NH \\ CH_2 \cdot CH(CN) \end{array} \longrightarrow \begin{array}{c} CH_2 \cdot CH_2 \\ | \qquad\quad >CO \\ CH_2 \cdot CH(CN) \end{array} \longrightarrow \begin{array}{c} CH_2 \cdot CH_2 \\ | \qquad\quad >CO \\ CH_2 \cdot CH_2 \end{array}$$
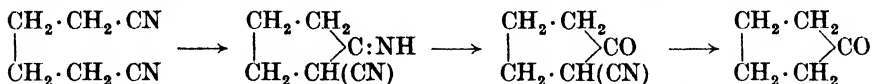
The synthesis of rings with more than six members cannot be effected so simply: if the carbon chain is long, the probability of the close approach of the two ends is small and the reaction takes place between the two nitrile groups, not of the same molecule, but of two different molecules, and leads to products of higher molecular weight. This difficulty has been overcome very ingeniously by K. Ziegler:[3] the condensing agent used was diethyl lithium amide, LiNEt₂, in ether, and the long-chain dinitrile was only allowed to enter in minute quantities at a time. The reaction thus proceeded at very low dilution; the probability of two molecules reacting

[1] Cf. E. F. J. Atkinson and J. F. Thorpe, *J.C.S.* 1906, **89**, 1906; 1907, **91**, 578.

[2] Ibid. 1909, **95**, 1901.

[3] K. Ziegler, H. Eberle, and H. Ohlinger, *Annalen*, 1933, **504**, 94.

together was reduced and that of intramolecular reaction consequently increased. By this modification a 52 per cent. yield of cycloheptadecanone, containing a ring of seventeen atoms, was obtained.

Nitriles of the type of acetonitrile and benzyl cyanide give trimolecular products if treated more vigorously with sodium ethoxide in alcoholic solutions. These are strongly basic compounds and are known as cyanalkines: for example that from acetonitrile is called cyanmethine and that from benzyl cyanide cyanbenzyline. They are amino-pyrimidine derivatives[1] and are formed by the interaction of the bimolecular compound with a further molecule of the nitrile.
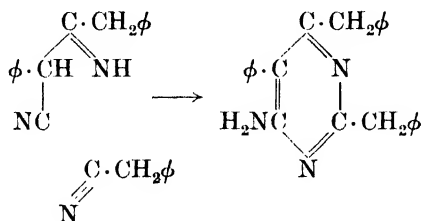
A nitrile such as benzonitrile, ϕCN, which contains no hydrogen atom in the α-position to the cyano group, cannot take part in these reactions and condensations. Nevertheless benzonitrile polymerizes to a trimolecular compound under the action of strong sulphuric acid: the polymer called cyaphenin is a triazine, as is shown by its formation in the action of sodium on a mixture of cyanuric chloride (p. 343) and bromobenzene.
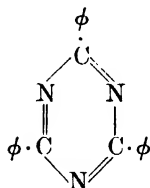
The polymerization is similar to that of the various derivatives of cyanic acid discussed below.

Isocyanides or Carbylamines

These compounds are isomeric with the nitriles and are sometimes called isonitriles. In the isocyanides the substituent is attached to nitrogen and their general formula is RNC. They were first prepared by A. Gautier in 1866 by the action of silver cyanide on alkyl iodides, a reaction which should be contrasted with that of potassium cyanide when the nitrile is the main product. Shortly afterwards Hofmann found that isocyanides were formed by the action of chloroform and alcoholic potash on primary amines:

$$R \cdot NH_2 + CHCl_3 \longrightarrow R \cdot NC + 3HCl.$$
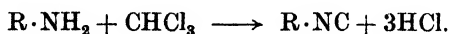
[1] E. von Meyer, *J. pr. Chem.* 1889, **39**, 156.

These two reactions are the most important methods of preparation. They are also sometimes formed as by-products in the preparation of nitriles.

The isocyanides are volatile liquids of great reactivity and with a very powerful and extraordinarily repulsive smell. A primary amine can be recognized to be such by warming a minute amount of it with chloroform and alcoholic potash. . The isocyanides boil at temperatures about 20° or 30° below the boiling-points of the isomeric nitriles and are scarcely soluble in water.

Isocyanides

						b.p.
Methyl isocyanide	.	.	.	.	.	59°
Ethyl isocyanide .	.	.	.	.	.	79°
n-Propyl isocyanide	.	.	.	.	.	98°
Phenyl isocyanide	.	.	.	.	.	166°

They are unstable compounds; the methyl compound has been known to explode and the phenyl compound decomposes on standing. They can be hydrolysed by water at 180° to formic acid and a primary amine, the intermediate stage being a substituted formamide:

$$R \cdot NC \longrightarrow RNH \cdot CO \cdot H \longrightarrow RNH_2 + HCO_2H.$$
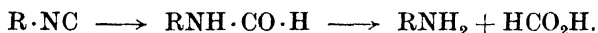
This reaction proves that the substituent R is attached to the nitrogen atom. They are hydrolysed with great rapidity by aqueous acids, sometimes almost explosively, but they are unaffected by alkalis. They behave to some extent as unsaturated compounds, a point discussed in detail below. Thus they absorb sulphur at temperatures above 100° and are converted into mustard oils, RNC $\longrightarrow$ RNCS; similarly, as Gautier found, they reduce mercuric oxide to metallic mercury and form iso-cyanates, RNC + HgO $\longrightarrow$ RNCO + Hg. They can be reduced, the aromatic ones by sodium and amyl alcohol and the aliphatic ones by hydrogen in the presence of nickel at 180°, to secondary amines, in which one of the groups is of necessity methyl: RNC $\longrightarrow$ RNH $\cdot$ CH$_3$. Finally if heated for some time rearrangement takes place and they are converted into true nitriles.

Although the constitution of these compounds is clearly indicated by their reactions, the state of combination of the carbon atom, which was for many years a matter of controversy, must now be discussed. In the early days when ideas about the pentavalency of nitrogen were rather vague, the formula was written R—N≡C. Such a formula is clearly extremely improbable: not only does it imply a pentacovalent nitrogen atom, but it assumes that a carbon atom can be united with another atom by all its four covalencies, a view which cannot be reconciled with what we know of the distribution in space of the carbon valencies. This formula was displaced by that of J. U. Nef,[1] who maintained that the carbon atom was divalent in the isocyanides and wrote the formula R—N=C⟨. This formula finds a certain amount of experimental sup-

[1] *Annalen*, 1892, **270**, 267; 1895, **287**, 265.

port; there is the oxidation to cyanic esters and the conversion into mustard oils by sulphur. Phenyl magnesium bromide will also add on to isocyanides to give, in poor yield, a compound $R \cdot N = C \diagdown_{MgBr}^{\phi}$ which on hydrolysis gives first the imine, $RN = CH\phi$, and finally benzaldehyde. All these reactions indicate that the unsaturation of an isocyanide is something to do with the carbon atom.

Nef's formula is not, however, satisfactory. It assigns a structure to the isocyanides which is that of a free radical, while the great majority of free radicals, such as those containing trivalent carbon, associate in pairs to a greater or smaller extent; further, the only known free radical containing divalent carbon, $H_2C\diagdown$ (see p. 354), is a body of very short life indeed. Now the isocyanides do not give bimolecular compounds, and are not even associated liquids, as is shown by the normal values of their Ramsay-Shields constants.[1] Nef's formula attributes too high a degree of unsaturation to the carbon atom. I. Langmuir[2] proposed the formula $R \cdot N \equiv C$, in which the nitrogen and carbon atoms are united by two co-valencies and a co-ordinate link formed by the 'lone pair' of electrons of the nitrogen atom. This formula implies that both atoms are surrounded by an octet of electrons, and can be written in any of the following ways, all of which are identical in meaning; in the last two the dots represent valency electrons.

$$R-N \overset{\rightarrow}{\equiv} C \qquad R-\overset{+}{N} \equiv \overset{-}{C} \qquad R : N \overset{\cdot}{\cdot} C : \qquad R : N :: C :$$
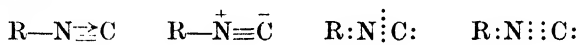
This formula fulfils every requirement for a satisfactory representation of the structure of these compounds.[3]

The more important points of the evidence in favour of this formula can be summarized as follows:

(i) In the Raman spectra of both methyl and ethyl isocyanides there is a strong band which must be attributed to the oscillation of the nitrogen and carbon atoms of the isocyano group.[4] The frequency of this oscillation lies in the region which experience has shown only includes those of the oscillations of atoms united by a triple link. Since a co-ordinate link is to all intents a single link, being formed by two electrons, this result would be predicted by Langmuir's formula.

(ii) The isocyanides are capable of forming co-ordinate compounds with certain metals, e.g. the platinous compounds

$$[Pt(MeNC)_2Cl_2] \quad \text{and} \quad [Pt(MeNC)_4]PtCl_4,[5]$$
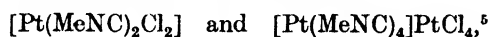
and in these the molecule acts as a donor of electrons, like an ammonia molecule, and never as an acceptor. With Langmuir's structure the

[1] H. Lindemann and L. Wiegrebe, *Ber.* 1930, **63**, 1650.

[2] *J. Amer. C. S.* 1919, **41**, 1543.

[3] D. Ll. Hammick, R. G. A. New, N. V. Sidgwick, and L. E. Sutton, *J.C.S.* 1930, 1876.   [4] A. Dadieu, *Ber.* 1931, **64**, 358.

[5] K. A. Hofmann and G. Bugge, ibid. 1907, **40**, 1774; L. Tschugaev and P. Teearu, ibid. 1914, **47**, 570.

carbon atom has a lone pair which can form a co-ordinate link to the metal, exactly as ammonia does. If Nef's formula were correct, the carbon atom has only six valency electrons, and it seems incredible that it should not complete its octet by acting as an acceptor.

(iii) From the heats of combustion of isocyanides,[1] the heat of rupture of the link between nitrogen and carbon can be calculated.[2] The mean value is 163 kg. cals.,[3] which is of the known order of magnitude for a triple link and almost identical with the value of 167 kg. cals. for the triple link in the nitriles.

(iv) The isocyanide grouping has an electric moment of about 3·6 D, and the carbon atom is negative with respect to the nitrogen: this is in accordance with the co-ordinate link structure. More convincingly, however, and this may be taken as a crucial test of the formula, the electric moment of *p*-diisocyanobenzene is indistinguishable from zero.[4] On the Nef formula the two carbon atoms of the isocyano groups cannot lie in the line joining the two nitrogen atoms, as we know from the space distribution of the oximes. Hence the moments of the two isocyano groups, if they had that structure, could not cancel out, since in only one of the possible configurations would the molecule have a centre of symmetry, and it is impossible that all the molecules can be in that one configuration all the time. On Langmuir's formula however, the molecule is symmetrical, since the N⇌C link is identical with a triple link in its stereochemical properties.
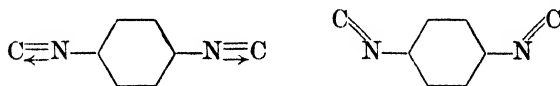
The chemical properties of the isocyanides find a ready explanation on the basis of Langmuir's formula. The nitrogen atom has all its valency electrons involved in bond formation while the carbon atom has an idle 'lone pair'. Hence the main reactivity of the group lies in the carbon atom.

The Constitution of Prussic Acid and its Salts

Prussic acid has two series of derivatives in which the carbon and nitrogen atoms are differently linked, the nitriles R—C≡N, and the isocyanides R—N⇌C. What then is the constitution of free prussic acid itself? Is it formonitrile, HCN, or the carbylamine HNC? This question has been debated in detail for many years and arguments of the most varied kind have been advanced. It is easy to find chemical reactions which can be interpreted as giving support to either view: examples have been quoted already. The physical properties have been interpreted in

[1] M. S. Kharasch, *Bur. Standards J.* 1929, **2**, 410.

[2] Hammick, New, Sidgwick, and Sutton, loc. cit.

[3] Calculated with the value of 169 kg. cals. for the heat of dissociation of the nitrogen molecule (see the Introduction).

[4] R. G. A. New and L. E. Sutton, *J.C.S.* 1932, 1415.

an equally ambiguous fashion. It has been claimed, for example, that the heat of combustion is quite inconsistent with the nitrile formula, and also that the refractivity makes the isocyanide structure impossible. The conclusion that has been generally accepted is that the compound is a tautomeric mixture of nitrile and isocyanide, and it is often quoted as the best known example of dyad tautomerism.[1] It should be noted that this view was accepted because of the difficulty of assigning one formula to the compound, which historically was how the idea of tautomerism arose, and not because there was any direct evidence that prussic acid in the liquid or gaseous states is a mixture of two isomers which can change into one another. Indeed attempts to obtain such evidence failed. The velocities of tautomeric change in a large number of cases are extremely sensitive to traces of other substances (see, e.g., p. 234), so that by working with very carefully purified vessels and compounds it has often been possible to reduce the rates of tautomeric change to such an extent that the tautomers can be separated by physical means, such as distillation. If this can be effected, there is, of course, conclusive evidence for tautomerism. No such evidence, however, can be found in the case of prussic acid.[2] This is no disproof of tautomerism: it merely indicates that if it is present, the rates of tautomeric change must be very high, which is not unlikely in such a simple molecule, or else that one tautomer is present only in a minute concentration. The values of the specific heat of gaseous hydrogen cyanide have been used as evidence for the existence of tautomerism,[3] but the argument carries little weight, partly because it is based on rather doubtful assumptions as to the specific heats of triatomic molecules and partly because, if the method is applied to acetylene, it indicates that that gas is a tautomeric mixture, which is not at all probable.

The study of the Raman spectrum of prussic acid[4] has, however, provided good evidence for the presence of the two different molecular species in the gaseous acid. The argument is peculiarly powerful because with such a simple molecule the possible oscillations are few. It shows two bands, one of which is much more intense than the other; the frequency which corresponds to the more intense band is that which would be expected for the oscillation of the carbon and nitrogen atoms in the molecule HCN from the known Raman frequencies of the nitriles, while the frequency from the weaker band agrees equally well with that to be expected from the molecule HNC from the Raman spectrum of the isocyanides. Hence both species must be present, but the amount of HNC cannot exceed 0·5 per cent. and is probably much smaller. We therefore can deduce that the acid in the liquid and gaseous states is a mixture of tautomers with a very high rate of tautomeric change.

In earlier years there was much discussion as to the structure of the salts of the acid, and it was debated whether they were cyanides or

[1] See J. W. Baker, *Tautomerism*, London, 1934, p. 69.
[2] K. H. Meyer and H. Hopff, *Ber.* 1921, **54**, 1709.
[3] E. H. Usherwood, *J.C.S.* 1922, **121**, 1604.   [4] A. Dadieu, *Ber.* 1931, **64**, 358.

isocyanides. With the alkali cyanides such a discussion has no point whatever. There is no covalent link between the alkali metal and either the carbon or nitrogen atom. The crystal of potassium cyanide has a structure very nearly the same as that of sodium chloride and is composed of potassium and cyanide ions.[1] The cyanide ion can only have one structure, which, with dots representing electrons, can be written $[:C \vdots N:]^-$, whether it is derived from the nitrile or isocyanide form of the acid. The cyanides of certain of the heavy metals, such as mercury and silver, do not, however, behave as electrolytes, and the metal is almost certainly covalently linked in the molecule. In their case the question of structure does arise, although no definite answer can be given. These salts differ from the alkali salts in several ways: they are not oxidized to cyanates by permanganate, and with alkyl halides they give almost entirely alkyl isocyanides, whereas the alkali salts give nitriles.

Cyanic Acid and its Derivatives

When an alkali cyanide is oxidized the product is the alkali cyanate which is derived from an acid to which the formula $HO—C≡N$, or the tautomeric formula $HN=C=O$, must be assigned. The more important derivatives of this acid are its acid halides, in which the hydroxyl group has been replaced by a halogen atom and which are often referred to as the cyanogen halides, its esters, which are derived from the imide structure and have the general formula $RN:CO$, and its amide, cyanamide, which is an important industrial product. These will be discussed in turn. Cyanic acid may be regarded as the mono-imide of carbonic acid and behaves as such in its hydrolysis to ammonia and carbon dioxide. It is formed in the oxidation of pure carbon by aqueous potassium permanganate in the presence of ammonia.[2]

Free cyanic acid is a very unstable compound. It is best prepared by heating its tripolymer, cyanuric acid $C_3H_3O_3H_3$, in a stream of dry carbon dioxide. Depolymerization takes place, and the gaseous cyanic acid can be condensed in a freezing mixture to a colourless very volatile liquid which is strongly acidic and raises painful blisters on the skin. Even below $0°$, however, the compound rapidly repolymerizes to a white amorphous polymer, cyamelide, while at higher temperatures and in the gas phase the tripolymer cyanuric acid is formed as well as cyamelide. The higher the temperature the greater the proportion of cyanuric acid.[3] The structure of cyanuric acid is known: it contains the tricyanogen ring and is discussed later. That of cyamelide has not been established with certainty. Cyamelide is formed to some extent in every reaction from which cyanic acid itself might be expected, e.g. the interaction of ammonia and carbonyl chloride, the decomposition of potassium cyanate with crystalline oxalic acid, and the thermal decomposition of urea. Cyamelide

[1] R. M. Bozorth, *J. Amer. C. S.* 1922, **44**, 317.   [2] G. Laude, *C.r.* 1930, **191**, 1135.
[3] E. A. Werner and W. R. Fearon, *J.C.S.* 1920, **117**, 1356.

forms no salts with the alkalis under any conditions, and hence it is very unlikely to contain hydroxyl groups or the amide grouping $\overset{|}{H}N-\overset{|}{C}=O$. It does, however, form a mercury derivative and hence may well contain imide groups $>C=NH$. If boiled with water it gives ammonia and carbon dioxide together with some cyanuric acid, and prolonged treatment with alkalis converts it into the alkali salt of cyanuric acid. On the basis of these properties A. Hantzsch[1] proposed the structure of a tripolymer in which a ring is formed of alternate carbon and oxygen atoms, cyanuric acid being the alternative ring-system of carbon and nitrogen atoms.

$$HN=\overset{O}{\underset{\overset{|}{O}}{C}} \quad \overset{}{\underset{\overset{|}{O}}{C}}=NH \longleftarrow 3HOCN \longrightarrow HO-\overset{N}{\underset{\overset{|}{N}}{C}} \quad \overset{}{\underset{\overset{|}{N}}{C}}-OH \quad \overset{NH}{\underset{}{CO}} \quad \overset{}{\underset{}{CO}}$$

Cyanuric acid
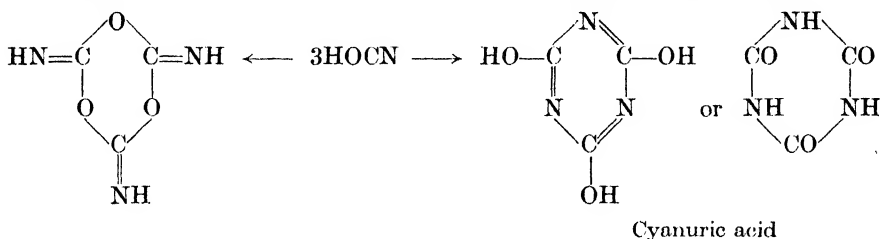
Cyamelide, however, is non-volatile and completely insoluble in any of the usual solvents. Its general behaviour is not that which would be expected from a compound of the molecular weight implied by Hantzsch's formula, but suggests that the compound is a linear polymer of high molecular weight. Hence a much more probable formula for cyamelide is one analogous to that of the polymerized forms of formaldehyde which Staudinger has shown to be linear polymers; i.e. the formula

$$\ldots \overset{NH}{\underset{}{-O-C}}-\overset{NH}{\underset{}{O-C}}-\overset{NH}{\underset{}{O-C}}-\ldots$$
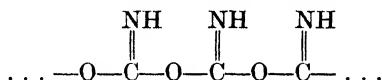
The nature of the terminal groups is not known: very probably the chain, which must contain a large number of cyanic acid units, has a hydroxyl group at each end which is formed from a trace of water present: this is known to be the case with one of the polymers of formaldehyde, α-poly-oxymethylene, in which the chain contains from forty to at least one hundred units.[2]

In aqueous solution cyanic acid is very rapidly hydrolysed to ammonia and carbon dioxide: as a secondary process some of the ammonia reacts with unchanged cyanic acid to give urea, as in Wöhler's synthesis of that compound. With the alcohols the acid reacts readily, the principal product being a carbamic ester (a urethane).

$$HOCN + ROH \longrightarrow H_2N \cdot CO \cdot OR$$
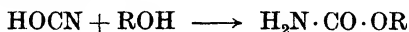
With amines substituted ureas are formed (see pp. 273 and 288). There is some evidence that in solution cyanic acid exists to a small extent in a dimeric form in equilibrium with the monomeric form.

$$2HNCO \rightleftharpoons H_2N \cdot CO \cdot N : C : O$$
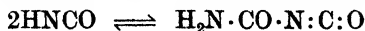
[1] *Ber.* 1905, **38**, 1013.　　[2] H. Staudinger and co-workers, *Annalen*, 1929, **474**, 175.

If an alcohol reacts with a solution of cyanic acid, there is always obtained a small amount of the allophanic ester, $H_2N \cdot CO \cdot NH \cdot CO_2R$, in addition to the carbamic ester. The allophanic ester clearly arises from the interaction of two molecules of the acid with one of the alcohol. Similarly, in the reaction with an amine (RNH_2) the main product is a substituted urea, $RNH \cdot CO \cdot NH_2$, but in addition a certain amount of the biuret,

$$RNH \cdot CO \cdot NH \cdot CO \cdot NH_2,$$

is formed. These facts have been interpreted as indicating the presence of a dimeric acid,[1] and this view is strengthened by the analogy with the amide of cyanic acid, which also polymerizes to a dimeric substance as well as to a cyclic triple polymer (see p. 329).

Of the salts of cyanic acid those of potassium and sodium can be prepared very easily by oxidation of the corresponding cyanide or ferrocyanide with manganese dioxide, litharge or dichromate, or by electrolytic oxidation of the aqueous cyanide solution. These alkali salts can be heated to redness without decomposition, but those of the alkaline earths and the heavy metals lose carbon dioxide on heating and are transformed into the metallic derivatives of cyanamide:

$$Ba(NCO)_2 \longrightarrow CO_2 + N \vdots C \cdot NBa.$$
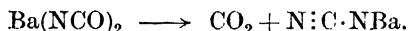
The alkali salts are stable in aqueous solution in the presence of free caustic alkali, which represses the salt-hydrolysis to free cyanic acid. In the absence of the free alkali, the cyanic acid is hydrolysed and the solution soon contains nothing but ammonia and the alkali carbonate, together with some urea formed from the ammonium and cyanate ions present in the solution. The rearrangement of the cyanates of ammonia and of primary and secondary bases into ureas is discussed on pp. 276 and 288.

Cyanic acid may have either of the tautomeric formulae $HO \cdot C \vdots N$ or $HN \vdots C \vdots O$, or may be a tautomeric mixture of the two; its true salts contain an anion for which the two formulae $[N \vdots C \cdot O^-]$ and $[O \vdots C \vdots N^-]$ can be written, and finally the metallic derivatives which, like that of mercury, do not behave as true salts and must be covalently linked compounds, may be related to either form of the acid and contain the metal attached either to oxygen or to nitrogen. The two formulae for the ion differ only in electronic distribution and hence cannot be distinguished from one another; thus, the ion must be to some extent a resonance-hybrid of the two formulae, but the contribution made by one structure may be greater than that made by the other. The evidence available is scanty and hardly sufficient to do more than indicate a probable answer to the questions these possibilities raise. The crystal structure of potassium cyanate has been investigated by S. B. Hendricks and L. Pauling,[2] and they have shown that the ion is straight with its three atoms in one line; both formulae for the ion predict on simple stereochemical grounds that it will

[1] T. L. Davis and K. C. Blanchard, *J. Amer. C. S.* 1929, **51**, 1806.
[2] Ibid. 1925, **47**, 2904.

be linear. The esters of cyanic acid are, as is discussed below, uniformly isocyanates, that is they are of the formula $RN:C:O$, and hence they provide a reference point for the covalently linked compounds. Now J. Goubeau[1] found that the Raman spectra of the esters, of the free acid, and of the mercury and silver salts were all very similar with a strong line at 1,300–1,400 cm.$^{-1}$ and two weak ones at 1,200 and 2,200 cm.$^{-1}$, while the Raman spectra of the potassium, tetramethylammonium, and lead salts were of a different type with two lines at 860 and 2,190 cm.$^{-1}$ This may be taken as evidence that the free acid has the structure $HN:C:O$ or is a tautomeric mixture in which that form predominates, and that the mercury and silver 'salts' are covalently linked N-compounds. The ion is clearly of a different structure and Goubeau deduces that it is the O-ion, $[N\!:\!C\cdot O^-]$. The crystal measurements already referred to indicate that there is little difference in the distances from carbon to nitrogen and carbon to oxygen, each being about 1·16 A. This probably means that there is not so great a distinction in the types of union as is indicated by the O-ion formula. The shortness of this distance suggests that the ion may be a resonance-hybrid of the two possible formulae.

When silver cyanate is treated with the free halogens at a low temperature in a suitable solvent (ether or ethyl chloride), unstable compounds of the type $Hal\cdot N:C:O$ can be obtained.[2] They polymerize readily to a dimeric form and finally a trimer, which is a derivative of cyanuric acid (I), since it is converted very readily into that acid by water or alkalis.
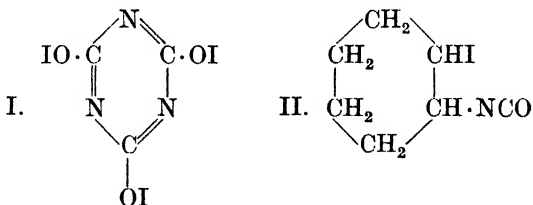
The iodo compound, $I\cdot NCO$, will add rapidly on to ethylenic compounds, and gives, for example, with cyclohexene, 2-iodocyclohexyl isocyanate (II). L. Birckenbach and H. Kolb[3] have made some remarkable observations on the course of the reaction which takes place between iodine, a cyanate, and cyclohexene in the presence of methyl alcohol. In all cases the isocyanate (II) is first formed. If the cyanate used is the silver salt or the ordinary mercury salt the final product is the carbamic ester (urethane), $R\cdot NH\cdot CO_2Me$, formed by the simple interaction of the methyl alcohol and the isocyanate. If, however, the cyanate is the tetramethyl-ammonium salt, the product is largely the allophanic ester,

$$R\cdot NH\cdot CO\cdot NH\cdot CO_2Me.$$

They interpret these results to mean that the cyanic acid liberated from

[1] *Ber.* 1935, **68**, 912.
[2] L. Birckenbach and M. Linhard, ibid. 1929, **62**, 2261; 1930, **63**, 2528, 2545.
[3] Ibid. 1933, **66**, 1571; 1935, **68**, 895.

the alkali salt is not the normal acid HNCO, but the unstable O-acid, HO·CN, which can react with the isocyanate much as any hydroxy compound does to give a substance from which the allophanic ester is formed.

$$R·N:C:O + HO·CN \longrightarrow RNH·CO·OCN \longrightarrow RNH·CO·N:C:O$$

$$\xrightarrow{\text{MeOH}} RNH·CO·NH·CO_2Me.$$
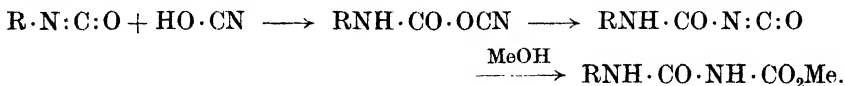
There is, however, no other evidence of the existence of two forms of cyanic acid, and until such is forthcoming, it is better to refrain from any precise deduction from observations on such a complex reaction.

The Cyanogen Halides

These compounds behave in the majority of their reactions as the acid halides of cyanic acid, although in other reactions they give rise to derivatives of hydrocyanic and not cyanic acid.

They are prepared by the action of the halogens on metallic cyanides or on hydrocyanic acid. Cyanogen bromide, which is used as a reagent, can be obtained in good yield by adding aqueous sodium cyanide to a cooled mixture of bromine and water.[1] Sometimes the halogen is produced *in situ* by adding sulphuric acid to a mixture of sodium bromate and bromide with sodium cyanide, and this method is the most convenient for preparing cyanogen chloride. The iodide is usually obtained by the action of an ethereal solution of iodine on silver or mercuric cyanide.

Cyanogen chloride is a colourless liquid, boiling at 15·5° and melting at −6°. The bromide is a colourless volatile solid (melting-point 52°, boiling-point 61°) and the iodide melts in a sealed tube at 146°, but in open vessels sublimes before melting. All the compounds are extremely poisonous. They are stable when pure, but polymerize rapidly to cyanuric halides (see p. 343) in the presence of traces of impurities. Examples of reactions in which they behave as halides of cyanic acid are the action of ammonia on cyanogen chloride when the amide cyanamide is formed, and the action of aqueous alkalis which hydrolyses the compounds to the alkali cyanate and halide:

$$BrCN + 2KOH \longrightarrow KOCN + KBr + H_2O.$$
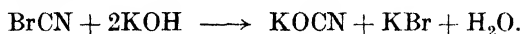
In other reactions, however, they behave as oxidizing agents: for example, cyanogen bromide liberates iodine quantitatively from aqueous hydriodic acid, and oxidizes sulphites to sulphates, hydrogen sulphide to sulphur, and hydroxylamine almost explosively to nitrogen. In reactions of this kind cyanic acid is not formed but its reduction product, hydrocyanic acid.

These oxidizing reactions have often been used as evidence for the view that in the cyanogen halides the halogen atom is attached to nitrogen and not to carbon, i.e. that their formula is not Hal·C:N but C⇌N·Hal. If this were so the compounds should be described as derivatives of fulminic acid, CNOH, and not of cyanic acid. Compounds containing a chlorine or

[1] K. H. Slotta, *Ber.* 1934, **67**, 1028; *Organic Syntheses*, vol. **11**, p. 30.

bromine attached to nitrogen are usually hydrolysed to hypochlorous or hypobromous acid, $>$NCl $\xrightarrow{\text{H}_2\text{O}}$ $>$NH + HOCl (see p. 41), and hence such a view will account for the oxidizing action. Even the hydrolysis of cyanogen chloride to a cyanate and a chloride could be explained on such a view by the assumption that the first hydrolysis product is the hypochlorite and cyanide, the latter being subsequently oxidized by the former. The interaction of cyanogen bromide with ammonia to give cyanamide could be brought into line by assuming that the carbon atom of the isocyanide structure reacts with the ammonia and then hydrogen bromide is eliminated:

$$\text{NH}_3 + \text{C}{\equiv}\text{N}\cdot\text{Br} \longrightarrow \underset{\text{H}}{\overset{\text{H}_2\text{N}}{>}}\text{C}{=}\text{N}\cdot\text{Br} \longrightarrow \text{H}_2\text{N}\cdot\text{CN} + \text{HBr}.$$
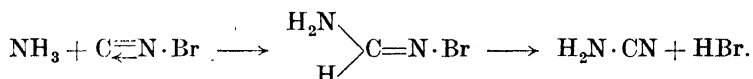
There are minor differences between the reactions of the chloride, bromide, and iodide and on this fact the suggestion has been made[1] that cyanogen chloride is an N-chloro compound, cyanogen iodide a C-iodo compound, and the bromide in solution a tautomeric mixture of the N-bromo and C-bromo compounds.

At the same time it must be remembered that some compounds are known which undoubtedly contain bromine attached to carbon but nevertheless give hypobromous acid on hydrolysis and act as oxidizing agents. Obvious examples are certain α-bromoketones which liberate iodine very readily from dilute aqueous hydriodic acid, a fact which is utilized in K. H. Meyer's method for estimating the enol in a keto-enol mixture. It is clear that we are dealing with one of the not infrequent cases where purely chemical arguments are incapable of settling the structure. The physical evidence is, however, decisive and shows that all the three compounds contain the halogen attached to carbon. The light absorption of the halides in the ultra-violet has been measured by R. M. Badger and S. C. Woo,[2] and is of the same type for all three compounds, a fact which makes any difference in structure between them very unlikely. The results show that there is a bond whose energy of dissociation is of the order of 97 kg. cal. for the iodide, 116 kg. cal. for the bromide and 125 kg. cal. for the chloride: this is too small to belong to the —C:N group but more than twice too large to belong to the N-halogen link whose energy of dissociation is known from measurements of compounds such as nitrosyl chloride. On the other hand, it is of the right order of magnitude for the C-halogen link, which must thus be present in the compounds.[3] Similarly the Raman spectrum of all three compounds is

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[1] E. V. Zappi, *Bull. Soc. chim.* 1930, **47**, 453, 537; E. V. Zappi and S. Elarza, ibid. 1931, **49**, 397.

[2] *J. Amer. C. S.* 1931, **53**, 2572.

[3] The heat of dissociation of N—Cl in NCl₃ is 39 kg. cal., and the normal value for C—Cl is 75 kg. cal., so the N—Cl link is very improbable. If we take the normal values for the heat of dissociation of the links between carbon and the halogens and

so similar[1] that they must all have the same structure. The Raman frequency for the nitrile and isocyanide groups are known from the simple members of those classes to be 2,245 and 2,180 cm.$^{-1}$, respectively, and it is further known that if a heavy atom is attached to a group, its characteristic Raman frequency is lowered. The observed principal Raman frequencies are Cl·CN 2,201, Br·CN 2,187, I·CN 2,158 cm.$^{-1}$. Hence the compounds cannot contain an isocyanide group and the halogen atom in them is attached to carbon.

Cyanogen bromide has been frequently used as a reagent in investigations on tertiary bases according to a method developed by J. von Braun.[2] Most tertiary bases will add on a molecule of cyanogen bromide giving an unstable ammonium compound which readily loses a molecule of alkyl bromide to leave a substituted cyanamide; the latter can be hydrolysed to the corresponding carbamic acid which immediately loses carbon dioxide.

$$\begin{array}{c} R \\ R' \\ R'' \end{array}\!\!\!>\!N + Br\cdot CN \longrightarrow \begin{array}{c} R \\ R' \\ R'' \end{array}\!\!\!>\!N\!-\!CN \, [Br]$$

$$\longrightarrow RBr + \begin{array}{c} R' \\ R'' \end{array}\!\!\!>\!N\cdot CN \longrightarrow \begin{array}{c} R' \\ R'' \end{array}\!\!\!>\!N\cdot CO_2H \longrightarrow \begin{array}{c} R' \\ R'' \end{array}\!\!\!>\!NH + CO_2$$
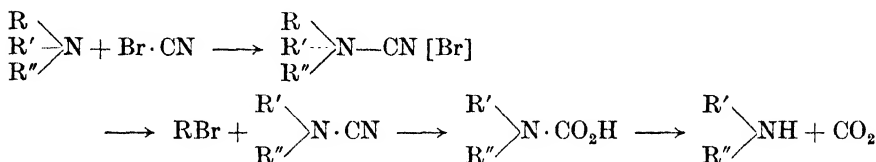
If one of the groups attached to the tertiary nitrogen atom is benzyl, this splits off as its bromide in preference to any other. The allyl group has the next greatest tendency to be split off and the other groups roughly in the order of their molecular weights. If the tertiary nitrogen atom is a member of a ring and the third group attached is neither benzyl nor allyl, the reaction very often leads to the opening of the ring to form a straight chain compound. Thus N-butylpiperidine can be converted into ε-brom-amyl-butylamine:

$$H_2C\!\!<\!\!\begin{array}{c} CH_2\!-\!CH_2 \\ CH_2\!-\!CH_2 \end{array}\!\!\!>\!N\cdot C_4H_9 \longrightarrow Br\cdot(CH_2)_5\cdot NH\cdot C_4H_9.$$
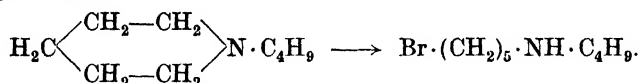
An example of this use of cyanogen bromide will be found in the work of K. Winterfeld and F. W. Holschneider[3] on the structure of the alkaloid lupinin.

compare them with those found for the cyanogen halides, there is a difference which is constant in the three compounds.

	obs.	calc.	diff.
Cl—CN	125	75	+50
Br—CN	116	62	+54
I—CN	97	45	+53

This may be due to an excess of energy contained in the CN fragment which is common to all three dissociations.

[1] W. West and M. Farnsworth, J. Chem. Phys. 1933, 1, 402.

[2] For references see Houben-Weyl, Die Methoden der organischen Chemie, 2nd ed., vol. iv, p. 323 et seq.   [3] Ber. 1931, 64, 137.

Cyanamide

Cyanamide, $N:C\cdot NH_2$, is the amide of cyanic acid, as is shown by its formation by the action of ammonia on cyanogen bromide. It can also be regarded as the nitrile of carbamic acid (see p. 271). In its tautomeric form, $HN:C:NH$, it would be the diimide of carbonic acid, but it does not possess this structure, although derivatives of this carbodiimide are known (see p. 292). It is best prepared by the action of freshly precipitated mercuric oxide on thio-urea in the presence of a little ammonium thiocyanate:

$$S:C(NH_2)_2 \longrightarrow H_2S + N:C\cdot NH_2.$$

It is also formed when carbon dioxide is passed over heated sodamide:

$$2NaNH_2 + CO_2 \longrightarrow NC\cdot NH_2 + 2NaOH.$$
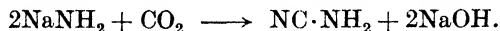
Cyanamide forms deliquescent colourless crystals melting at 41° and is easily soluble in water, alcohol, and ether. It behaves as a weak base forming with strong acids salts which are easily hydrolysed, but it is also an acid, both of its hydrogen atoms being replaceable by metals.

In alkaline solution ($p_H > 12$) cyanamide is quantitatively hydrolysed to urea, the velocity of the reaction[1] being proportional to the concentration of the anion $NC\cdot NH^-$. The urea, of course, can be further hydrolysed to ammonia and carbon dioxide. If the hydrogen-ion concentration of the solution lies between 10^{-8} and 10^{-12}, the cyanamide polymerizes rapidly to the so-called dicyandiamide or dicyanamide which is cyanoguanidine, $HN:C(NH_2)\cdot NH\cdot CN$ (see p. 295). The reaction is of the second order and takes place between a cyanamide anion and an undissociated molecule: it occurs rapidly within these limits of hydrogen-ion concentration because, the acid dissociation constant of cyanamide being $2\cdot1 \times 10^{-9}$, both ions and undissociated molecules are present in appreciable amounts. Cyanamide is quite stable in aqueous solutions in which the hydrogen-ion concentration is of the order of 10^{-5}, i.e. faintly acid. Cyanamide takes up hydrogen sulphide to form thio-urea, and reacts with ammonia to give guanidine:

$$N:C\cdot NH_2 + NH_3 \longrightarrow HN:C(NH_2)_2.$$

It will react with alcohols in the presence of mineral acids to give O-substituted ureas:

$$N:C\cdot NH_2 + ROH \longrightarrow HN:C(NH_2)OR.$$

If an ammoniacal solution of silver nitrate is added to an aqueous cyanamide solution, a yellow precipitate of silver cyanamide, $NC\cdot NAg_2$, is formed. This reacts with ethyl iodide to give silver iodide and diethyl cyanamide, $NC\cdot NEt_2$, the constitution of which is shown by the fact that it yields diethylamine if boiled with dilute acids, and also by its formation from diethylchloramine and potassium cyanide:

$$Et_2NCl + KCN \longrightarrow Et_2N\cdot CN.$$
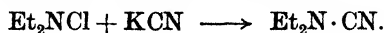
[1] G. H. Buchanan and G. Barsky, *J. Amer. C. S.* 1930, **52**, 195.

Comparison of the molecular refractivities of this and similar compounds with that of cyanamide itself and with that of dipropylcarbodiimide, $PrN:C:NPr$, shows that cyanamide resembles its dialkyl compounds in structure and is not carbodiimide: its formula must be $NC \cdot NH_2$.[1]

Of the metallic derivatives of cyanamide, the calcium salt is very important from a technical point of view. Its formation is the basis of one of the methods whereby atmospheric nitrogen can be brought into chemical combination and thus made available for use as a fertilizer in agriculture and as a source for other nitrogen compounds.[2] After the discovery by Moissan in 1892 that metallic carbides can be obtained in the electric furnace, several attempts were made to cause these carbides to combine with atmospheric nitrogen mainly with the idea of obtaining cyanides. The protracted investigations of A. Frank and N. Caro led in 1898 to the result that, whereas barium carbide would absorb nitrogen at a high temperature to give a mixture containing barium cyanide, calcium carbide when pure absorbs no nitrogen even at 1,200°, but in the presence of lime rapidly forms calcium cyanamide. Later they found that superheated steam will hydrolyse calcium cyanamide to ammonia and in 1901 began experiments on the direct application of the compound to the soil as a nitrogen fertilizer. From those observations there has developed an enormous industry. In 1906 no synthetic nitrogen manures were used, only ammonium sulphate from the coal-gas industry and Chile saltpetre: in 1929 nearly a million and a half tons of nitrogen in the form of calcium cyanamide were used in agriculture throughout the world, a quantity which is 10·8 per cent. of the total nitrogen and 18·2 per cent. of the synthetic nitrogen so used. The cyanamide industry was one of the first to produce an adequate synthetic nitrogen fertilizer, and in the years 1912–15 provided about 60 per cent. of the total synthetic nitrogen: processes such as Haber's synthesis of ammonia from its elements have become formidable competitors, but the world production of calcium cyanamide has increased steadily. The manufacture needs large quantities of energy for the electric furnaces in which both the carbide is made and the nitrogen absorbed: hence the first factories were established in Italy, France, and Norway, and also at the Niagara Falls. During the Great War there was an enormous expansion of the industry in Germany, which became isolated from its former supplies of combined nitrogen, and the capacity of its calcium cyanamide factories increased from 10,000 tons of nitrogen in 1914 to 100,000 tons in 1918.

The mechanism of the absorption of nitrogen by calcium carbide is still unknown. Although the pure carbide absorbs no nitrogen, absorption is rapid at 1,050° in the presence of 10 per cent. of calcium oxide. Other compounds such as sodium chloride· and the chloride and fluoride of

[1] E. Colson, *J.C.S.* 1917, **111**, 554.

[2] An interesting account, from which some of the facts quoted are drawn, will be found in 'Der Kalkstickstoff in Wissenschaft, Technik und Wirtschaft', by H. H. Franck, W. Makkus, and F. Janke, *Ahrens' Sammlung*, Stuttgart 1931.

calcium act as catalysts and are used. The crude product contains an excess of carbide which is decomposed by addition of the correct amount of water. After this treatment the fertilizer, often called 'Kalkstickstoff', contains 58–60 per cent. of calcium cyanamide (i.e. 20–21 per cent. of combined nitrogen), 9–12 per cent. of free carbon, mostly graphite, and 20–28 per cent. of lime together with a certain amount of silica. There has been great controversy about the origin of the toxic effect which the fresh substance sometimes has on plants, but used rightly it is a valuable fertilizer. It has none of the poisonous action of prussic acid and its salts, but has its own specific effect on man in that it dilates the blood-vessels and thus vastly increases the effect of substances such as alcohol or caffeine on the system. In consequence cases have occurred where an agricultural labourer has suffered from refreshing himself with beer after scattering the substance on the fields: no permanent damage, however, has been observed.

Besides its use in agriculture, calcium cyanamide has been used as a source of compounds such as urea and cyanides: the latter can be obtained by fusing it with sodium chloride at 1,200° and extracting the cooled melt with water.

The Esters of Cyanic Acid

Of the two possible series of esters of cyanic acid, the cyanates $RO \cdot CN$ and the isocyanates $O:C:NR$, only the latter are known, while with the corresponding thiocyanic acid, both series of esters can be obtained. The true cyanates are most probably formed by the action of a sodium alcoholate on a cyanogen halide, but the product is the polymer, the normal cyanurate.

$$RO \cdot Na + Cl \cdot CN \longrightarrow RO \cdot CN \longrightarrow$$
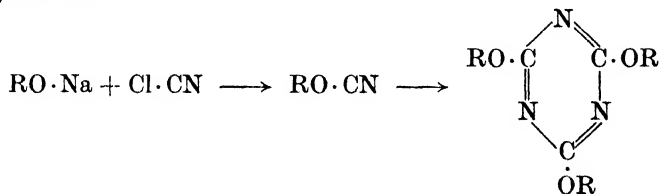
The isocyanic esters are well known. They were first prepared by A. Wurtz in 1854 by distilling the salts of alkyl sulphuric acids with potassium cyanate, and led him to the discovery of the simple primary amines.

$$EtO \cdot SO_2 \cdot OK + K \cdot NCO \longrightarrow EtN \cdot CO + K_2SO_4$$
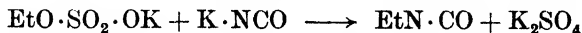
The yields of isocyanate obtained by this method are small because a large fraction of the product polymerizes. A better method for preparing the aliphatic esters is to heat potassium cyanate with the appropriate dialkyl sulphate in the presence of dry sodium carbonate:[1] if the alkyl sulphate is inaccessible, the p-toluene sulphonic ester, formed by the action of the sulphonic chloride on the alcohol in the presence of pyridine, can be used.

[1] K. H. Slotta and L. Lorenz, *Ber.* 1925, **58**, 1320.

Isocyanic esters are formed by the action of carbonyl chloride on amines: the carbamyl chloride is an intermediate product and loses hydrogen chloride:

$$\text{COCl}_2 + \text{RNH}_2 \longrightarrow \text{HCl} + \text{Cl·CO·NHR} \longrightarrow \text{HCl} + \text{OCNR.}$$
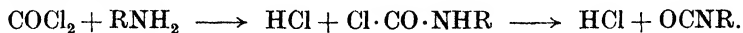
Phenyl isocyanate is usually made in this way, phosgene being passed over aniline hydrochloride at 200°, or heated with the hydrochloride in benzene under pressure at 120°. Another general method of preparation is to obtain the N-substituted urethane from an amine and chloroformic ester and distil it with phosphoric anhydride:

$$\text{RNH}_2 + \text{Cl·CO}_2\text{Et} \longrightarrow \text{RNH·CO}_2\text{Et} \longrightarrow \text{RN:C:O.}$$

Other reactions in which they are formed are those between silver cyanate and an alkyl iodide, the oxidation of isocyanides with mercuric oxide, the Hofmann reaction for the conversion of an amide into an amine (see p. 146), and the decomposition of acyl azides which rearrange with loss of nitrogen to isocyanates when heated in an indifferent solvent (see p. 375).

The structure of these esters is established as RN:C:O by their methods of formation and their hydrolysis by mineral acids and alkalis to an amine and carbon dioxide. They are volatile liquids of a powerful and unpleasant smell, which when quite pure can be kept for months without change. Small amounts of impurities, notably salts such as sodium acetate, however, cause them to polymerize fairly rapidly to tripolymers, the esters of isocyanuric acid (see p. 344). Apart from their hydrolysis the more important reactions of the esters involve addition to the C=N group. Thus with hydroxy compounds, such as alcohols of all types and phenols, an ester of carbamic acid (a urethane) results: and with primary and secondary amines a substituted urea.

$$\text{RN:C:O} + \text{R'OH} \longrightarrow \text{RHN·CO}_2\text{R'}$$
$$\text{RN:C:O} + \text{R'NH}_2 \longrightarrow \text{RHN·CO·NHR'}$$
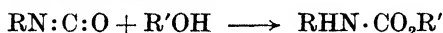
These additions take place with great ease, and consequently phenyl isocyanate has often been used both as a reagent for the detection of the hydroxyl and amino groups and also for the identification of alcohols, since the N-phenylurethanes are solid derivatives easily isolated and purified. A classical example of the use of this reagent is the work of H. Goldschmidt[1] in which he showed that the two isomeric oximes of benzaldehyde and benzil were both hydroxy compounds (see p. 176). α-Naphthyl isocyanate is sometimes used in preference to the phenyl ester, because the urethanes and ureas derived from it are less soluble and hence tests can be carried out with smaller quantities.[2] In the presence of water isocyanic esters give symmetrically substituted ureas, since a part of the ester is hydrolysed to the amine which combines with the

[1] *Ber.* 1889, **22**, 3101.
[2] V. T. Bickel and H. E. French, *J. Amer. C. S.* 1926, **48**, 747; H. E. French and A. F. Wirtel, ibid. 1736.

unchanged ester: thus phenyl isocyanate gives diphenylurea, and in conse-
quence water must be rigidly excluded when the isocyanate is used as a
reagent, $\phi \cdot NCO \longrightarrow \phi NH_2 \longrightarrow \phi NH \cdot CO \cdot NH\phi$. The esters also
react with carboxylic acids: the principal products are carbon dioxide and
the substituted amide of the acid:

$$R \cdot CO_2 H + \phi NCO \longrightarrow R \cdot CONH\phi + CO_2.$$
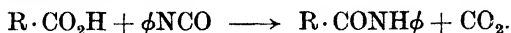
Thiocyanic Acid and its Derivatives

Salts of thiocyanic acid can be obtained from the cyanides by direct
combination with sulphur, just as those of cyanic acid are formed by the
oxidation of cyanides. The free acid is found in the stomach of man,
and its salts occur in the urine and saliva of animals and in plant tissues.
The technical source of thiocyanates is the water used for washing coal-gas,
from which ammonium thiocyanate can be obtained.

The free acid is best obtained by the action of potassium bisulphate on
potassium thiocyanate.[1] At room temperatures it is a gas whose pro-
perties closely resemble those of hydrogen chloride: it is freely soluble in
water to give an acid solution, and fumes with gaseous ammonia. It has
none of the characteristic poisonous action of prussic acid. It is not,
however, very stable and is slowly converted into a yellow solid even if
kept in carefully dried glass vessels. If the carefully dried gas is cooled
to $-30\text{-}40°$, it condenses to colourless crystals which are considerably
less stable than the gaseous compound: at $0°$ they rapidly become yellow
and change into a syrupy liquid which evolves gas and leaves a reddish
amorphous solid. This change is much accelerated by traces of water.
Molecular weight determinations show that thiocyanic acid is mono-
molecular in nitrobenzene and benzene. In dilute aqueous solution it is
fairly stable at $0°$, but if such a solution is heated or if a concentrated
solution is prepared, polymerization takes place; hydrogen cyanide is
formed and the so-called perthiocyanic acid, $H_2C_2N_2S_3$, separates out.
This compound should be referred to as isoperthiocyanic acid, since,
although it is an acid, the structure of its salts is quite different from that
of the compound itself: in German it is called 'Xanthanwasserstoff'. When
it is treated with alkalis, sulphur first separates and then dissolves again
to form the salt of the true perthiocyanic acid. The constitution of the
compound and of the salts has been shown to be as follows:[2]

| | Isoperthiocyanic acid | | Potassium perthiocyanate |

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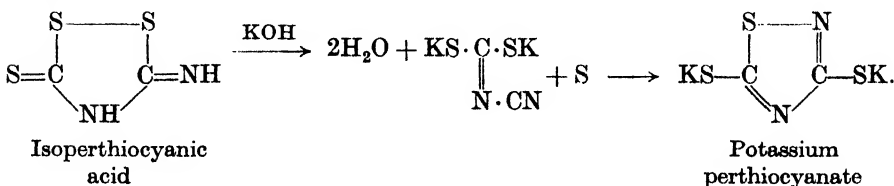
[1] U. Rück and H. Steinmetz, Z. anorg. Chem. 1912, 77, 51, where a full discussion
of the various methods of preparation is given.

[2] A. Hantzsch and M. Wolverkamp, Annalen, 1904, 331, 265.

If a fairly concentrated solution of thiocyanic acid is heated with excess of sulphuric acid, it is hydrolysed and the main products are ammonia and carbon oxysulphide:

$$HSCN + H_2O \longrightarrow COS + NH_3.$$

With hydrogen sulphide, carbon disulphide and ammonia are produced,

$$H_2S + HSCN \longrightarrow CS_2 + NH_3$$

a reaction which probably accounts for the presence of the traces of carbon disulphide found in certain plants. The reaction is reversible since carbon disulphide reacts with excess of ammonia in alcoholic solution to give ammonium thiocyanate and sulphide, and this affords a convenient method for obtaining the ammonium salt. The partial transformation of this salt into thio-urea and at a higher temperature into guanidine thiocyanate is discussed elsewhere (pp. 290 and 295). An important extension of the former transformation is the reaction of thiocyanic acid with amino-aldehydes or amino-ketones[1] which leads to mercapto-glyoxalines: the free amino group of the thio-urea undergoing ring closure with the carbonyl group:
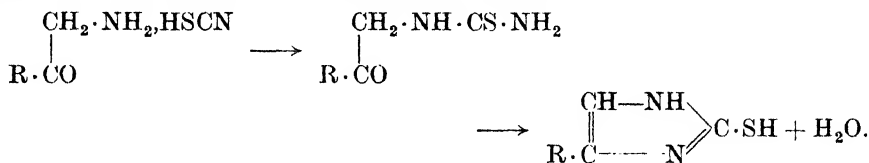
The salts of thiocyanic acid give with solutions containing the ferric ion the well-known deep blood-red coloration which can be extracted with ether. This test is very delicate, a thousandth of a milligram of ferric ion producing a visible pink colour. The coloured substance is the complex ion $[Fe(SCN)_6]'''$, as is shown by the fact that the red colour migrates to the anode on electrolysis and that the red so-called ferric thiocyanate, which is ether-soluble, shows a molecular weight in ether and benzene which corresponds to the formula $Fe[Fe(SCN)_6]$ rather than to $Fe(SCN)_3$.[2]

The characteristic extraction of the colour by ether seems to be due to the great solubility of $Fe[Fe(SCN)_6]$ in ether: if excess of a soluble thiocyanate is added to an aqueous solution of this salt, the colour is no longer extracted by ether, because all the iron is converted into the complex ion $[Fe(SCN)_6]'''$.[2]

The actual constitution of free thiocyanic acid is not known with certainty: it can have either of the alternative structures $HS \cdot C:N$ or $S:C:NH$, of which the former is the more probable. The thiocyanate ion $[SCN]^-$ is known to be linear from the X-ray analysis of thallium thiocyanate,[3] and the two alternative structures $N \equiv C - S^-$ and $^-N = C = S$ are, of course, both linear. As with the cyanate ion these structures differ only

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[1] S. Gabriel and G. Pinkow, *Ber.* 1893, **26**, 2201; F. L. Pyman, *J.C.S.* 1911, **99**, 668.

[2] H. L. Schlesinger and H. B. van Valkenburgh, *J. Amer. C. S.* 1931, **53**, 1212.

[3] M. Strada, *Gazz.* 1934, **64**, 400.

in electronic distribution and are indistinguishable, but there is evidence that in the resonance-hybrid of the two the structure $N\equiv C—S^-$ predominates. Careful comparison of its Raman spectrum with those of cyanogen chloride and carbon oxysulphide[1] shows that there is a resemblance between $N\equiv C—S^-$ and $N\equiv C—Cl$, both showing the oscillation of the triply linked carbon and nitrogen atoms, but that there is no oscillation frequency in the ion belonging to the doubly linked carbon and sulphur atoms as there is in $O=C=S$, and there would be in $^-N=C=S$.

While only one series of esters of cyanic acid can be obtained, both series of the esters of thiocyanic acid are known, the thiocyanic, $RS \cdot C:N$, and the isothiocyanic esters, $R \cdot N:C:S$. The latter group are usually called the mustard oils, since the allyl ester can be obtained from mustard seed; they are more stable than the true thiocyanic esters in that distillation often converts an alkyl thiocyanate into a mustard oil.

The alkyl thiocyanates ($RS \cdot C:N$) are liquids of garlic-like smell and can be obtained by the action of alkyl iodides or dialkyl sulphates on potassium thiocyanate, and by the action of cyanogen chloride on the mercaptans:

$$R \cdot SH + Cl \cdot CN \longrightarrow RS \cdot CN.$$

That they contain the alkyl group attached to sulphur and not to nitrogen is shown by their reduction to a mercaptan and prussic acid, and by their oxidation by nitric acid to the alkyl sulphonic acids. They are hydrolysed by alcoholic potash to potassium thiocyanate, which is never formed in the alkaline hydrolysis of a mustard oil. The ease with which they undergo isomeric change into the mustard oil varies with the nature of the alkyl group. Methyl thiocyanate must be heated to 180° for several hours before the change is complete, but the allyl ester shows the typical ready migration of the allyl group and is converted into the mustard oil in one distillation. If traces of mineral acid are present, the isomeric change does not take place, but the esters polymerize to the thiocyanuric cyclic tripolymers.

Compounds containing the thiocyanic group in the α-position to a carbonyl group rearrange and condense intramolecularly to give derivatives of thiazole. Thus thiocyanoacetone on heating with sodium carbonate gives methyl-hydroxy-thiazole.

$$CH_3 \cdot CO \cdot CH_2 \cdot SCN \longrightarrow$$
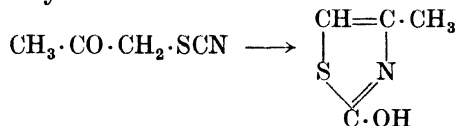
Similarly, internal condensation can take place with a carboxyl group. Thio-cyanacetic acid if treated with hydrochloric acid is first hydrolysed to carbamyl-thioglycollic acid which on further heating closes the thiazolidine ring.

$$NCS \cdot CH_2 \cdot CO_2H \longrightarrow H_2N \cdot CO \cdot S \cdot CH_2 \cdot CO_2H \longrightarrow$$
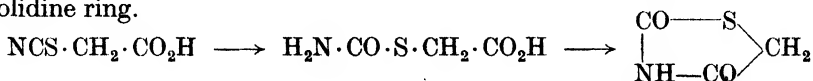
[1] A. Langseth, J. U. Sörensen, and J. R. Nielsen, *Z. phys. Chem.* 1934, B, **27**, 100.

The aromatic thiocyanates, such as phenyl thiocyanate, present few features of interest. They can be obtained by the action of potassium thiocyanate on a diazonium salt, or sometimes it is better to use cuprous thiocyanate as well in a modified Sandmeyer reaction. The thiocyano group can be introduced by direct substitution into phenols and amines either by the use of free thiocyanogen (see p. 302), or by an ingenious use of cupric thiocyanate. This salt breaks down in the presence of water to cuprous thiocyanate and the hydrolysis products of thiocyanogen: but in the absence of water and the presence of an easily substituted aromatic compound the thiocyanogen set free in the decomposition brings about substitution in the nucleus.[1]

$$2Cu(SCN)_2 + \phi\cdot NH_2 \longrightarrow 2CuSCN + HSCN + NCS\langle\ \rangle NH_2$$
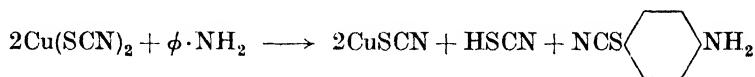
The o-amino thiocyanates do not exist, but pass at once into amino-benzthiazoles, certain of which act as powerful local anaesthetics.
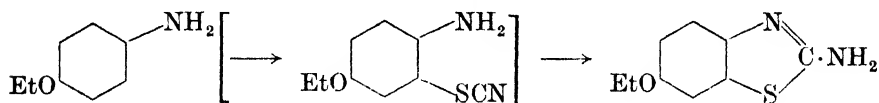
The aromatic thiocyanates show no tendency to rearrange into mustard oils on heating.

The isothiocyanic esters or mustard oils are liquids of an unpleasant odour; they distil without decomposition and are insoluble in water. As mentioned above, their name is derived from allyl isothiocyanate which can be obtained from black mustard, and which occurs in a number of plants, especially those belonging to the order *Cruciferae*. The mustard seeds contain a complex compound known as sinigrin or potassium myronate which has the structure[2]

$$CH_2{=}CH\cdot CH_2\cdot N{=}C\langle^{S\cdot C_6H_{11}O_5}_{O\cdot SO_3K}\ ;$$
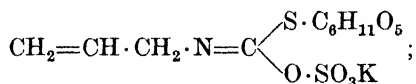
it may be regarded as a derivative of the hypothetical imino-thiocarbonic acid $HN{:}C(OH)SH$ and is at the same time a glucoside and a sulphate. The seeds also contain an enzyme, myrosin, which can hydrolyse the glucoside to allyl isothiocyanate, glucose, and potassium hydrogen sulphate. Hydrolysis with potassium methoxide yields *l*-thioglucose.[3] Other natural mustard oils are known; these contain different alkyl groups, and in some of their glucosides the potassium is replaced by a nitrogenous base. The more important methods of obtaining the mustard oils in the laboratory involve the use of an amine, which is clear indication of the structure of

[1] H. P. Kaufmann and K. Küchler, *Ber.* 1934, **67**, 944.

[2] J. Gadamer, ibid. 1897, **30**, 2322.

[3] W. Schneider and F. Wrede, ibid. 1914, **47**, 2225.

these compounds. A simple example is the condensation of a primary alkylamine with thiophosgene:[1]

$$R \cdot NH_2 + Cl_2CS \longrightarrow R \cdot NCS + 2HCl.$$
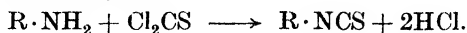
The best-known preparation of the alkyl compounds is from carbon disulphide and a primary amine; these condense to the amine dithiocarbamate, from which the silver salt can be obtained by the action of silver nitrate. This salt decomposes on boiling with water to silver and hydrogen sulphides and a mustard oil:

$$CS_2 + 2H_2N \cdot Et \longrightarrow [\overset{+}{N}H_3Et]\overset{-}{S} \cdot CS \cdot NHEt]$$

$$2Ag \cdot S \cdot CS \cdot NHEt \longrightarrow Ag_2S + H_2S + 2EtNCS.$$
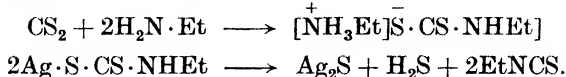
The dithiocarbamate can also be decomposed to the mustard oil by heating with mercuric or ferric chlorides.

The aromatic mustard oils can also be obtained from the primary aromatic amines and carbon disulphide. If these are heated together (see p. 51) the product is a thio-urea and not a dithiocarbamate: the thio-urea is converted into the mustard oil by boiling with strong hydrochloric acid. A small amount of a triaryl-guanidine is formed at the same time (see p. 298).

$$2\phi \cdot NH_2 + CS_2 \longrightarrow \phi NH \cdot CS \cdot NH\phi \overset{HCl}{\dashrightarrow} \phi NCS + \phi NH_2, HCl$$

If, however, the aromatic amine and carbon disulphide react in the presence of alcoholic ammonia, the ammonium salt of the dithiocarbamic acid crystallizes out, and is conveniently converted into the mustard oil by addition of a solution of lead nitrate: this is the best way of preparing phenyl isothiocyanate:[2]

$$\phi NH_2 + CS_2 + NH_4OH \longrightarrow \phi NH \cdot CS \cdot SNH_4$$

$$\overset{Pb(NO_3)_2}{\dashrightarrow} \phi NCS + PbS + HNO_3 + NH_4NO_3.$$
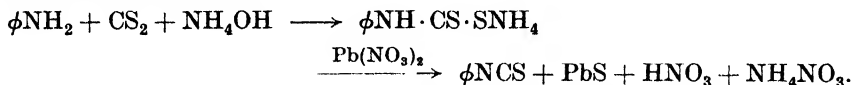
Hofmann's mustard oil test for primary amines is based on the reactions discussed above. It consists of boiling the amine with carbon disulphide in the presence of mineral acid. Tertiary amines do not react while secondary amines give dithiocarbamates which cannot break down to mustard oils. The formation of a mustard oil is recognized by its smell, so that the test fails if it is not easily volatile; in this case it is hydrolysed by the acid.

The reactions of the mustard oils run parallel with those of the isocyanates. They are hydrolysed by dilute acids to a primary amine, carbon dioxide, and hydrogen sulphide, and by concentrated sulphuric acid to the amine and carbon oxysulphide. They show the same kind of addition reactions, giving thio-ureas with ammonia and primary and secondary amines, and thio-urethanes with aliphatic alcohols, but not with phenols or alcohols of the type of benzyl alcohol.

$$\phi NCS + RNH_2 \longrightarrow \phi NH \cdot CS \cdot NHR \quad : \quad \phi NCS + ROH \longrightarrow \phi NH \cdot CS \cdot OR$$
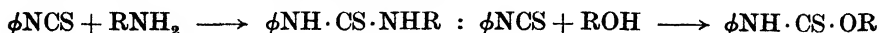
[1] G. M. Dyson and R. F. Hunter, *Rec. trav. chim.* 1926, **45**, 421.

[2] *Organic Syntheses*, Collective vol. 1, p. 437.

They have been used for the preparation of a variety of heterocyclic compounds. On reduction they yield different products according to the reagent used: thus phenyl mustard oil is reduced by aluminium amalgam in ether to methyl mercaptan and aniline, which condenses with unchanged mustard oil to give diphenyl thio-urea, while ethyl mustard oil is reduced by zinc and sulphuric acid to ethylamine and thioformaldehyde which appears as its trimolecular polymer: $3EtNCS \longrightarrow 3EtNH_2 + (HCHS)_3$.

Fulminic Acid[1]

In 1800 when the nature of hydrochloric acid was quite obscure and the existence of the element chlorine had not been established, E. Howard[2] attempted to synthesize mercuric chloride by the action of ethyl alcohol and excess of nitric acid on mercuric nitrate. Instead of the expected product he obtained greyish white crystals which detonated violently when struck or when treated with concentrated sulphuric acid. This was the first preparation of mercuric fulminate. J. von Liebig, who had been interested in fulminates since as a boy he had seen a pedlar in Darmstadt making small quantities of mercuric fulminate and selling it as a kind of firework, showed in 1823 that silver fulminate, which can be obtained in a manner similar to the mercury derivative, had the same composition as silver cyanate. This was the first discovery of two compounds of the same composition but quite different properties, and it was in connexion with this example that J. J. Berzelius invented the word isomerism.

Howard's original method is still the source of mercuric fulminate, which is manufactured on a commercial scale and used in detonators for initiating the explosion of explosives of both types, the slow-burning propellants such as cordite and the fracturing high explosives such as dynamite and trinitrotoluene. It can be detonated either by shock, as in the cartridge of a rifle, or by heat, as in an electrically operated exploder or a burning fuse. Its explosion is so violent that it is not used alone but mixed with some substance such as potassium chlorate or antimony sulphide. The other salts of fulminic acid are obtained from the mercuric or silver salt; thus sodium amalgam and the mercury salt shaken together under water give an aqueous solution of sodium fulminate. The latter is a true salt and gives solutions which show electrolytic conductivity, but the mercury salt, as in many other cases, is a non-electrolyte and the metal is covalently linked.

Free fulminic acid is not known in the pure state. An ethereal solution containing it can be obtained[3] by extraction with ether of an aqueous solution of the sodium salt which has been acidified with sulphuric or oxalic acid. If the ethereal solution is distilled at 0°, the distillate contains fulminic acid, as is shown by the formation of the silver salt with

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[1] A useful monograph on this subject is 'Die Knallsäure', H. Wieland, *Ahrens'* *Sammlung*, 1909, vol. **14**, p. 385.

[2] *Phil. Trans.* **90**, 204.   [3] H. Wieland and H. Hess, *Ber.* 1909, **42**, 1346.

silver nitrate. The free acid can thus exist in the vapour state, and may well be a gas at room temperatures when pure. Polymerization of the acid takes place very readily both in aqueous and ethereal solution to a variety of products which are mentioned below. The smell of the acid is very similar to that of hydrocyanic acid, a fact which has led to several misunderstandings in the past; both the acid and its salts are violently poisonous, their action resembling that of cyanides, and as a final point of similarity both the mercury and silver salts are sparingly soluble both in water and nitric acid.

Owing to the explosive nature of the salts, some of which will explode under water on rubbing with a glass rod, and to the instability of the free acid, the investigation of the constitution of the acid was not easy and it was some time before the question was settled. For many years the molecular weight of the acid was in doubt since no volatile derivatives whose vapour density can be measured are known. Since it could be obtained from ethyl alcohol, for a long time it was thought to contain two carbon atoms in the molecule and the formula was written $C_2N_2O_2H_2$. The first observation that threw light on the constitution was made simultaneously by A. Steiner[1] and E. Carstanjen and A. Ehrenberg,[2] and was that the sole products of the action of strong hydrochloric acid on a fulminate are formic acid and hydroxylamine hydrochloride. This shows that the compound must be regarded as an oxime or oxime derivative, and in consequence Steiner proposed the structure di-oximinoethylene, $HON:C:C:NOH$. This formula, though satisfactory in some ways, leaves certain facts without any reasonable explanation. It was the American J. U. Nef[3] who realized that this formula is based on a false molecular weight for the acid and who collected the experimental evidence in support of the formula which, with a slight modification, is accepted to-day. The more important indications that the molecular formula is CNOH and not twice this are:

(i) No acid salts of fulminic acid are known, and hence it is unlikely to be dibasic.

(ii) In its decomposition with hydrochloric acid the carbon-containing product is formic acid with only one carbon atom, and hence the compound is unlikely to contain linked carbon atoms.

(iii) Mercuric fulminate can be obtained by the decomposition of a compound containing only one carbon atom: if the sodium salt of nitromethane is treated with mercuric chloride in ice-cold aqueous solution, the fulminate is precipitated. This would appear to be a simple loss of water:

$$H_2C{=}N{\diagup O}^{O}_{\diagdown Ohg} \longrightarrow H_2O + C{=}NO{\cdot}hg \quad (hg{=}\tfrac{1}{2}Hg).$$
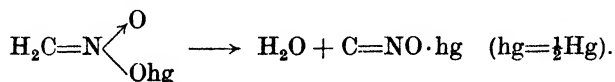
This view receives strong support from the behaviour of aqueous solutions of the sodium salt.[4] If the acid is CNOH, the salt is a binary electrolyte,

[1] Ibid. 1883, **16**, 1484. [2] *J. pr. Chem.* 1882, **25**, 232.

[3] *Annalen,* 1894, **280**, 305. [4] L. Wöhler, *Ber.* 1905, **38**, 1351.

while if it is $C_2N_2O_2H_2$, the salt must dissociate into three ions. Which of these is the truth is indicated by the depression of the freezing-point of the solvent, since the apparent molecular weight in the one case is $\dfrac{CNONa}{2}$ and in the other $\dfrac{C_2N_2O_2Na_2}{3}$; hence Wöhler obtained clear evidence for the simpler formula. Similarly it is known that at 0° the molecular conductivity of a salt of a monobasic acid increases on passing from N/32 to N/1,024 solution by 4–8 reciprocal ohms, while that of a salt of a dibasic acid increases by about 11. The observed increase for sodium fulminate is 5.

Nef thus represented fulminic acid as the oxime of carbon monoxide, C:NOH, and stated that it resembled the isocyanides in containing 'bivalent carbon'. It should thus show an unsaturation of the carbon atom similar to that of the isocyanides, and this is true. Fulminic acid and hydrogen chloride form an addition product[1] which must be the chloride of formhydroxamic acid, $\dfrac{H}{Cl}{>}C{=}NOH$, since it reacts with aniline to give formanilidoxime (phenyl isuretin) identical with the product obtained from isuretin (see p. 201) and aniline.

$$HON{=}C{<}^{H}_{Cl} \longrightarrow HON{=}CH\cdot NH\phi \longrightarrow HONH\cdot CH{=}N\phi$$

$$HONH\cdot CH{=}NH + \phi NH_2 \longrightarrow HONH\cdot CH{=}N\phi + NH_3$$
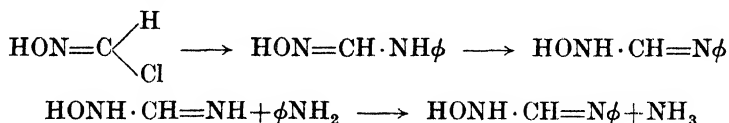
The existence of this compound explains very clearly the hydrolysis of fulminic acid by hydrochloric acid: formhydroxamic chloride is first formed which then is hydrolysed normally to formic acid and hydroxylamine: $Cl\cdot CH:NOH \longrightarrow HO\cdot CH:O + H_2NOH$. There is no doubt about the essential truth of Nef's view, but his formula should be emended to correspond with that of the isocyanides which has been discussed above; mercuric fulminate[2] should thus be written $(C{\equiv}NO)_2Hg$.

Just as isocyanides tend to rearrange to cyanides, fulminic acid derivatives rearrange to cyanic derivatives. Thus all attempts to prepare the acyl derivatives by the action of acid chlorides give acyl isocyanic acids, $C:NO\cdot COR \longrightarrow O:C:N\cdot COR$, and the action of alkyl halides on silver fulminates does not give the esters of fulminic acid, which are unknown, but alkyl isocyanates, $C:NOR \longrightarrow O:C:NR$.

Other reactions in which fulminic acid is formed support Nef's structure. Methyl nitrolic acid decomposes in the presence of silver nitrate to give silver fulminate, $O_2N\cdot CH:NOH \longrightarrow HNO_2 + CNOAg$, a reaction which is reversible in that treating fulminic acid with nitrous acid gives the nitrolic acid.[3] This decomposition of the nitrolic acid is the final step in the complicated series of changes involved in Howard's original method of preparation, which has been elucidated by Wieland.[4] The alcohol is

[1] R. Scholl, *Ber.* 1894, 27, 2816.   [2] See N. V. Sidgwick, *Chem. Rev.* 1931, 9, 77.
[3] H. Wieland, *Ber.* 1907, 40, 418.   [4] loc. cit.

first oxidized to acetaldehyde, hence the latter gives a better yield. The aldehyde is converted by the nitrous acid into oximino-acetaldehyde, which is oxidized to oximino-acetic acid. This compound is known to undergo nitration and loss of carbon dioxide in the presence of nitrous fumes to give methyl nitrolic acid, which reacts with the mercuric nitrate to give mercury fulminate:

$$CH_3 \cdot CH_2OH \longrightarrow CH_3 \cdot CHO \longrightarrow HON:CH \cdot CHO \longrightarrow HON:CH \cdot CO_2H$$
$$\longrightarrow HON:C(NO_2) \cdot CO_2H \longrightarrow HON:CHNO_2 \longrightarrow HONC.$$
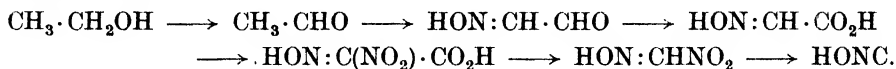
Scholl's interesting synthesis of aromatic aldoximes[1] is a reaction between an aromatic hydrocarbon and mercuric fulminate in the presence of anhydrous and hydrated aluminium chloride. The reaction almost certainly involves formhydroxamic chloride, formed by addition of hydrogen chloride from the aluminium salt to fulminic acid, and is of the Friedel-Crafts type: $HON:CHCl + \phi H \longrightarrow HON:CH \cdot \phi + HCl$. Yields up to 70 per cent. can be obtained, but the presence of hydrated aluminium chloride is essential: in its absence the product is not the aldoxime, but the nitrile $\phi \cdot CN$. This is not formed by dehydration of the oxime, which is stable under the conditions of reaction, but by a Friedel-Crafts reaction of cyanogen chloride, $Cl \cdot CN$, which is formed from fulminic acid or form-hydroxamic chloride in the absence of the hydrated aluminium chloride: $ClCH:NOH \longrightarrow Cl \cdot CN + H_2O$.

The last reaction of the fulminic acid that will be mentioned is with the halogens.[2] Fairly stable monomolecular addition products are formed, the oximes of di-halogen substituted formaldehydes, $Hal_2C:NOH$. Of these the chlorine compound is the most stable, while the iodine compound dissociates reversibly. On distillation they decompose into hypohalogen acid and cyanogen halide: $Cl_2C:NOH \longrightarrow ClCN + HOCl$. The salts of fulminic acid behave differently towards the halogens.[3] The primary addition product loses metallic halide and the intermediate nitrile oxide polymerizes to a furoxane, as would be expected (see p. 345).

$$2Br_2CONhg \longrightarrow HgBr_2 + 2(Br \cdot CNO) \longrightarrow$$
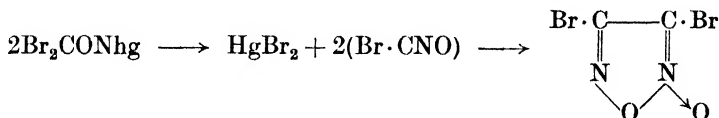
The polymerization of fulminic acid is a complicated subject which has been extensively studied by Wieland and his co-workers.[4] Only the main facts can be stated here. The polymerization proceeds more slowly in solutions containing mineral acids,[5] and thus possibly involves the fulminate ion. The tripolymer, metafulminuric acid, is the best known, and has been shown to be oximino-isoxazolone oxime (I): this is formed in

[1] *Ber.* 1899, **32**, 3492; 1903, **36**, 10, 322, 648.

[2] L. Birckenbach and K. Sennewald, *Annalen*, 1931, **489**, 7; *Ber.* 1932, **65**, 546.

[3] H. Wieland, ibid. 1909, **42**, 4198.

[4] Summarizing paper, *Annalen*, 1929, **475**, 54.

[5] L. Birckenbach and K. Sennewald, ibid. 1934, **512**, 45.

quantity if an ethereal solution of fulminic acid is allowed to stand. At the same time a small amount of the tetrapolymer, isocyanilic acid, is formed: this is known to be the dioxime of furoxane dialdehyde (II).

$$\text{I.} \quad \begin{matrix} \text{HC}\!-\!\!-\!\text{C}\!=\!\text{NOH} \\ \| \qquad | \\ \text{N} \quad \text{C}\!=\!\text{NOH} \\ \diagdown \text{O} \diagup \end{matrix} \qquad \text{II.} \quad \begin{matrix} \text{HON:CH}\cdot\text{C}\!-\!\!-\!\text{C}\cdot\text{CH:NOH} \\ \| \qquad \| \\ \text{N} \qquad \text{N} \\ \diagdown \text{O} \diagup \diagdown \text{O} \end{matrix}$$
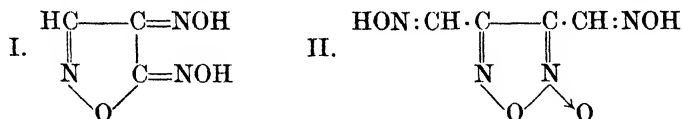
When mercury fulminate is boiled with potassium chloride solution, it gives the salt of another tripolymer, fulminuric acid, as Liebig discovered. This acid has been shown to be nitro-cyanacetamide,[1]

$$\text{O}_2\text{N}\cdot\text{CH(CN)}\cdot\text{CONH}_2.$$

Cyanuric Acid and its Derivatives

Of the various types of polymerization shown by the cyanogen derivatives there is one which is common to several classes, the formation of a tripolymer containing the 1,3,5-triazine ring, which consists of three carbon and three nitrogen atoms arranged alternately. Most of the derivatives of cyanic and thiocyanic acid can be converted into polymers of this kind, as well as certain nitriles such as benzonitrile, $\phi\cdot\text{CN}$, and cyanoformic ester, $\text{NC}\cdot\text{CO}_2\text{Et}$, which are unable to polymerize to cyanalkines (see p. 317). The majority of these polymers, being formed from compounds in which a group is attached to carbon, have the structure (I), but the polymer of

$$\text{I.} \quad \begin{matrix} \text{R} \\ \text{C} \\ \diagup \diagdown \\ \text{N} \quad \text{N} \\ \| \qquad | \\ \text{R}\cdot\text{C} \quad \text{C}\cdot\text{R} \\ \diagdown \diagup \\ \text{N} \end{matrix} \qquad \text{II.} \quad \begin{matrix} \text{OH} \\ \text{C} \\ \diagup \diagdown \\ \text{N} \quad \text{N} \\ \| \qquad | \\ \text{HO}\cdot\text{C} \quad \text{C}\cdot\text{OH} \\ \diagdown \diagup \\ \text{N} \end{matrix} \qquad \text{III.} \quad \begin{matrix} \text{O} \\ \text{C} \\ \diagup \diagdown \\ \text{HN} \quad \text{NH} \\ | \qquad | \\ \text{OC} \quad \text{CO} \\ \diagdown \diagup \\ \text{NH} \end{matrix}$$
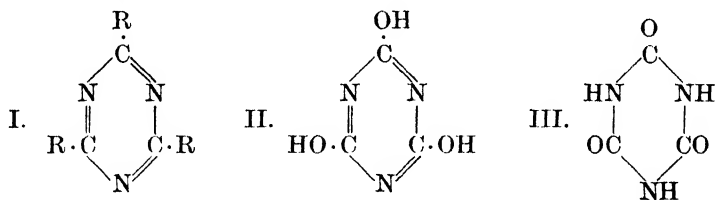
cyanic acid can clearly exist in the two tautomeric forms (II) and (III) (as well as possible intermediate forms), and derivatives of both of these structures are known. Prussic acid itself does not give a tripolymer of this type and the parent substance triazine itself (I, R = H) is unknown.

The truth of this heterocyclic structure for the cyanuric compounds was accepted before any concrete evidence in its support had been found, because of the ready explanation it gave for the composition and behaviour of the compounds. It is, however, strongly supported by the following facts:

(a) Under the right conditions the three chlorine atoms of cyanuric chloride (I, R = Cl) can be replaced one at a time by amino groups by means of ammonia or primary amines. By the successive use of ammonia, methylamine, and ethylamine the compound (IV) (methyl ethyl melamine) is

[1] M. Conrad and A. Schulze, Ber. 1909, **42**, 735.

formed, and in whatever order the three reagents are used the product is the same.[1] This is strong support for the view that the three chlorine
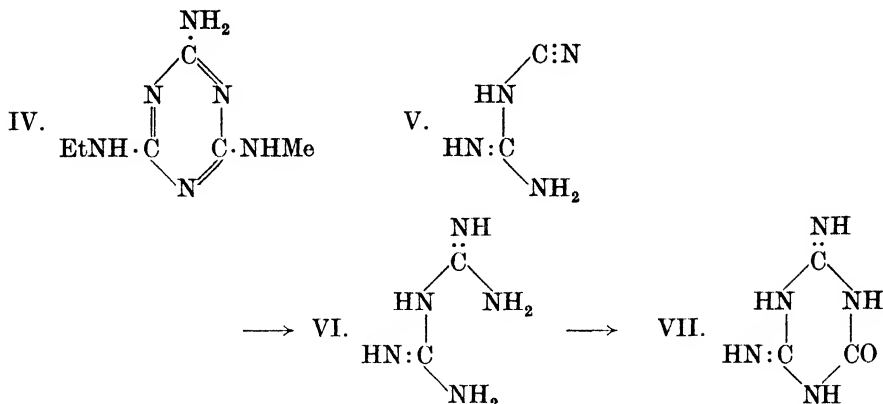
atoms occupy identical positions, which is hardly possible except in a ring structure.

(b) In one case the triazine ring has been built up in stages through intermediates of known structure. Cyanoguanidine (V: see p. 329) reacts with ammonia to give biguanide (VI) which further reacts with diethyl carbonate to form ammeline (VII) identical with the product of the partial hydrolysis of melamine (I, R = NH_2).

Cyanuric acid (II and III) is formed in the spontaneous polymerization of cyanic acid together with cyamelide (see p. 322) from which it can be separated by extraction with hot water, and crystallizes from this as a dihydrate. It has no melting-point, but volatilizes on heating as cyanic acid. It is best prepared in a pure state by the action of water on cyanuric bromide. It is hydrolysed by hot mineral acids to carbon dioxide and ammonia, but is stable to caustic alkalis, with which it forms salts. It is a very weak acid, and is monobasic when titrated with phenolphthalein as indicator. The di-sodium salt can be obtained with excess of caustic soda, and the sparingly soluble tri-sodium salt by boiling with caustic soda. The latter salt is decomposed by carbon dioxide with formation of the mono-salt. Whether the constitution of the acid is best represented by (II) or (III) is not easy to decide: with diazomethane at a low temperature the tri-N-methyl ester is formed, a fact which indicates the lactam structure (III). A. Hantzsch found that the acid did not react with dry ammonia and hence described it as a pseudo-acid, one whose salts have a structure different from that of the free acid. He allotted (III) to the acid and a formula derived from (II) to the salts.

Cyanuric chloride and bromide (I, R = Cl or Br) are best obtained by the polymerization of the corresponding cyanogen halide in the presence of a little free halogen: they are also formed by the action of the phosphorus pentahalide on cyanuric acid. The chloride melts at 145° and boils at

[1] O. Diels, ibid. 1899, 32, 692.

190°, but the bromide is a white powder which does not melt below 300°. Both the O-esters derived from (II) and the N-esters derived from (III) are known. The former are best obtained by the action of sodium alkoxide on cyanuric chloride or bromide. Their constitution is shown by the fact that on hydrolysis cyanuric acid and an alcohol are formed. The tri-O-methyl ester melts at 135° and boils at 265°, at which temperature it is slowly converted into the tri-N-methyl ester, a behaviour common to all the O-esters. The N-esters resemble the O-esters in physical properties, but are hydrolysed to primary amines and carbon dioxide, showing that they are derived from (III). They are formed by the polymerization of isocyanic esters, RNCO, and are often called isocyanuric esters. A. Hantzsch and H. Bauer[1] state that they prepared esters of a mixed type such as the di-O-mono-N-methyl ester, but later work has failed to confirm this result,[2] and shown that, as is often the case in organic chemistry, only the symmetrical esters, either the tri-O or the tri-N, can be obtained. The amide of cyanuric acid (I, R = NH_2) is called melamine and is formed by the action of ammonia on the halides and O-esters of cyanuric acid and also by the action of heat on the dipolymer of cyanamide, the so-called 'dicyandiamide' (see p. 295). It is sparingly soluble in cold water, and behaves as a monacidic base. In addition to these triazine derivatives, others are known which are not formed by any polymerization: an example is cyanuric triazide $C_3N_3(N_3)_3$ prepared by the action of sodium azide on cyanuric chloride, which is very explosive but crystallizes very well from alcohol. The interaction of cyanogen bromide and sodium azide gives a dimolecular product dicyanodiazide, $CN \cdot N : C(N_3)_2$, formerly regarded as cyanogen azide or carbon pernitride.[3]

The polymerization products of thiocyanic acid and its derivatives are very similar to those of cyanic acid, with the marked exception that the S-esters are much more stable than the N-esters.

Nitrile Oxides

The nitrile oxides are a small group of compounds isomeric with the isocyanic esters. Our knowledge of the group is largely due to Wieland,[4] who suggested for their structure the formula $R—C{=}N$. A more probable $\diagdown O \diagup$ structure, however, is the straight chain $R \cdot C{\equiv}N{\rightarrow}O$, a point which is discussed below. The compounds are unstable, polymerizing with ease into a variety of products, and the only ones known are aromatic derivatives, such as benzonitrile oxide, $\phi \cdot CNO$, and the carbethoxy derivative $EtO_2C \cdot CNO$, the so-called oxalic ester nitrile oxide.

If benzhydroxamic chloride is treated with aqueous sodium carbonate at 0°, benzonitrile oxide can be obtained as colourless needles melting at

[1] Ber. 1905, **38**, 1006.   [2] K. H. Slotta and R. Tschesche, ibid. 1927, **60**, 301.
[3] C. V. Hart, J. Amer. C. S. 1928, **50**, 1922.
[4] Ber. 1907, **40**, 1667; 1909, **42**, 803.

15° and with a characteristic smell.[1] The same compound can also be obtained by the spontaneous decomposition of benzonitrolic acid[2] (p. 241).

$$\phi \cdot C \underset{NOH}{\overset{Cl}{<}} \longrightarrow \phi \cdot C \vdots NO \qquad \phi \cdot C \underset{NOH}{\overset{NO_2}{<}} \longrightarrow \phi \cdot C \vdots NO + HNO_2$$
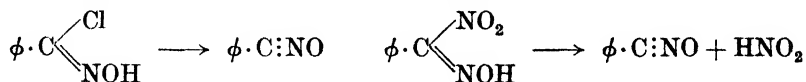
Oxalic ester nitrile oxide was obtained by R. Scholl and A. Schöfer[3] as colourless needles, melting-point 111–111·5°, by the interaction of bromacetic ester and silver nitrite: some nitroacetic ester is formed which decomposes with loss of water.

$$EtO_2C \cdot CH_2NO_2 \longrightarrow EtO_2C \cdot CNO$$
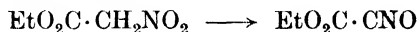
When triphenylmethyl chloride reacts with silver fulminate, triphenylmethyl nitrile oxide, $\phi_3C \cdot C \vdots N \rightarrow O$, is formed, and not the ester of fulminic acid, $C \vdots NO \cdot C\phi_3$.[4] This, however, is not a general reaction, since with halides other than that of triphenylmethyl the product is an isocyanate and not a nitrile oxide.[5]

In neutral solution the nitrile oxides polymerize readily to bimolecular products, the furoxanes (the so-called glyoxime peroxides), which can also be obtained by oxidation with hypochlorite of the γ-dioximes of α-diketones, and are known to have the structure shown.[6]

$$2\phi CNO \longrightarrow \underset{\underset{O}{\overset{\displaystyle N}{\;}} \overset{\phi \cdot C - C \cdot \phi}{\underset{N}{\;\;\;\;\;}} O}{} \longleftarrow \underset{NOH \;\; NOH}{\phi \cdot C - C \cdot \phi}$$
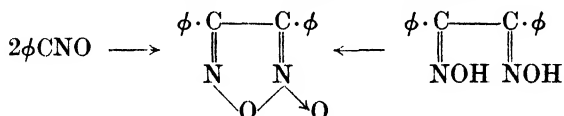
In acid solution another product is obtained, the so-called dibenz-oxoazoxime, which probably has the structure

$$\underset{\phi \cdot C = N}{\overset{O \leftarrow N = C \cdot \phi}{\underset{|}{\;\;\;\;\;\;}}} \Big\rangle O$$
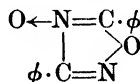
Finally in alkaline solution a polymer is obtained which, unlike the other two, shows the same reactions as the unpolymerized nitrile oxide, and in this recalls the relationship between cyanic and cyanuric acids. Wieland hence concludes that it is a triple polymer: its structure may be

$$\phi \cdot C \underset{O \swarrow}{\overset{O \nwarrow}{<}} \underset{N = C}{\overset{N - C}{\underset{\phi}{\overset{\phi}{<}}}} \Big\rangle N \rightarrow O.$$
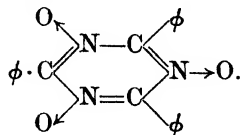
The nitrile oxides can be reduced quantitatively to nitriles: with methyl

[1] A. Werner and H. Buss, *Ber.* 1894, **27**, 2199; H. Wieland, ibid. 1907, **40**, 1670.

[2] H. Wieland, ibid. 1909, **42**, 803.   [3] Ibid. 1901, **34**, 876.

[4] H. Wieland and B. Rosenfeld, *Annalen*, 1930, **484**, 236.

[5] H. Wieland and A. Höchtlen, ibid. 1933, **505**, 237.

[6] J. Meisenheimer, H. Lange, and W. Lamparter, ibid. 1925, **444**, 97; C. R. Kinney, *J. Amer. C. S.* 1929, **51**, 1592.

magnesium iodide a ketoxime is formed, and mineral acids hydrolyse them
to some extent to hydroxylamine and a carboxylic acid.

$$\phi CNO + CH_3MgI \longrightarrow \begin{array}{c} \phi \cdot C \cdot CH_3 \\ \| \\ NOH \end{array}$$

$$\phi CNO + 2H_2O \longrightarrow \phi \cdot CO_2H + NH_2OH$$
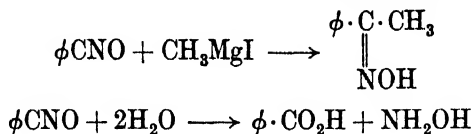
The triple polymer is a somewhat explosive solid which on heating in an
inert solvent rearranges to an isocyanate; if it is heated with aniline the
same change seems to take place, since the normal product of the inter-
action of aniline and an isocyanate, a substituted urea, is formed. Apart
from their polymerization, the nitrile oxides behave as comparatively
saturated compounds: it was on these grounds that Wieland preferred the
cyclic to the straight chain formula. The cyclic formula, however, seems
unlikely on stereochemical grounds and finds no support in the spectro-
chemical data.[1] Hence until further evidence is available, the straight
chain structure seems the more probable.

[1] K. v. Auwors, *Ber.* 1928, **61**, 1041.

CHAPTER XI

ALIPHATIC DIAZO COMPOUNDS AND DERIVATIVES OF HYDRAZOIC ACID

THE ALIPHATIC DIAZO COMPOUNDS

THE aliphatic diazo compounds contain the characteristic group $>CN_2$; thus diazomethane has the formula CH_2N_2 and diazoacetic ester $CHN_2 \cdot CO_2Et$. This group does not form salts with either acids or bases. The name is, perhaps, unfortunate since they differ from the aromatic diazo compounds in constitution, and resemble them only in a few reactions. The first member of the class to be obtained, diazoacetic ester, was prepared by T. Curtius in 1883. The simplest member, diazomethane, was obtained by von Pechmann in 1894.

The more important methods for the preparation of aliphatic diazo compounds are as follows:

(1) H. von Pechmann's method,[1] which has been used for diazomethane and diazoethane. An N-nitroso compound can be obtained from methyl (or ethyl) urethane by the action of nitrous acid (see p. 274): it is a yellow liquid which can be distilled under reduced pressure. If its ethereal solution is warmed with methyl alcoholic potash, it is hydrolysed and a yellow liquid distils which is an ethereal solution of the gaseous diazomethane.

$$EtO \cdot CO \cdot NHCH_3 \xrightarrow{HNO_2} EtO \cdot CO \cdot N(CH_3)NO$$
$$\xrightarrow{H_2O} EtOH + CO_2 + [CH_3 \cdot NH \cdot NO] \longrightarrow CH_2N_2 + H_2O$$
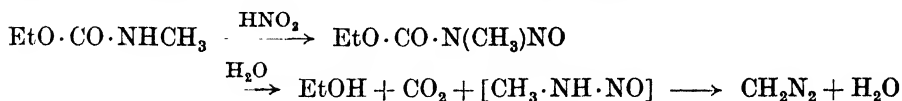
This method for obtaining diazomethane has been largely displaced by the more convenient modification introduced by F. Arndt and J. Amende.[2] Methylurea can be prepared from methylamine hydrochloride and potassium cyanate and is more accessible than methylurethane: with nitrous acid it gives an N-nitroso derivative which, like the urethane, is hydrolysed by caustic potash with the formation of diazomethane (see p. 289).

Considerable light is thrown on the course of the hydrolysis of nitrosomethylurethane by the work of A. Hantzsch and M. Lehmann.[3] They found that if the hydrolysis is carried out with concentrated aqueous caustic potash at 0°, a white potassium salt separates, which is unstable and decomposes in damp air or on addition of a little water to give diazomethane and caustic potash. Analysis shows that the composition of the salt corresponds with the formula $CH_3 \cdot N:N \cdot OK,H_2O$. If potassium ethylate in ethyl alcohol is used, a corresponding salt containing a molecule of alcohol, $CH_3 \cdot N:N \cdot OK,EtOH$, can be obtained. The solvent of

[1] *Ber.* 1894, **27**, 1888; 1895, **28**, 855.
[2] *Z. angew. Chem.* 1930, **43**, 444; *Organic Syntheses*, 1935, **15**, 3.
[3] *Ber.* 1902, **35**, 897.

crystallization cannot be removed from these salts, because on standing or warming decomposition into diazomethane takes place. The salts appear to be the analogues of the aromatic diazotates (see p. 409), a view which is supported by the fact that during their decomposition, particularly in the case of the alcoholate, nitrogen is evolved as well as diazomethane: the salt thus has two modes of decomposition,

$$CH_3 \cdot N:N \cdot OK, ROH \begin{cases} \nearrow & CH_2N_2 + KOH + ROH \\ \searrow & CH_3OR + KOH + N_2 \end{cases}$$
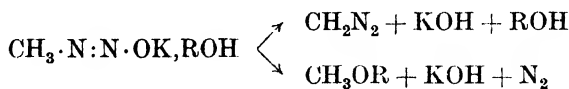
and the one that involves loss of nitrogen is exactly paralleled by the decomposition of an aromatic diazotate in the presence of alcohol with the production of the ethyl ether and nitrogen. The fact that the hydrate of the potassium salt will crystallize from aqueous caustic potash, but is rapidly decomposed by water, indicates that the acid from which the salt is derived is very weak. With a large excess of the base the salt is stable, but in water it is hydrolysed with production of the free acid which immediately decomposes. The corresponding sodium salt has been prepared by J. Thiele[1] by a reaction which is a general one for obtaining diazotates. Nitroso-methylhydrazine is treated in methyl alcoholic solution with caustic soda and an alkyl nitrite, moisture and carbon dioxide being carefully excluded. Nitrous oxide is evolved and the sodium diazotate crystallizes out.

$$CH_3 - \underset{\underset{NO}{|}}{N} - NH_2 + HNO_2 + NaOH \longrightarrow CH_3 - \underset{\underset{NO}{|}}{N} - N:N - ONa$$

$$\longrightarrow CH_3 - N = NONa + N_2O$$
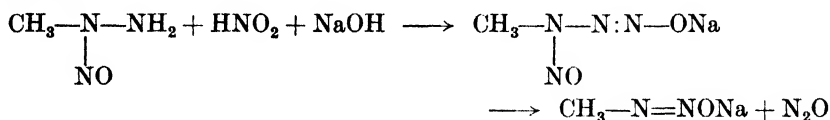
The salt explodes in moist air, but can be converted into diazomethane by passing a stream of dry carbon dioxide through its suspension in dry ether.

There is another method for preparing aliphatic diazo compounds which is somewhat similar to that of von Pechmann, but capable of much wider application.[2] Many primary aliphatic amines form addition compounds with mesityl oxide, $Me_2C:CH \cdot COMe$, which, as secondary amines, give N-nitroso compounds with nitrous acid; these latter are liquids which can be purified by distillation under reduced pressure. They are hydrolysed by an alcoholic solution of a sodium alkoxide (isopropyl or isobutyl alcohols give the best results) to mesityl oxide and an aliphatic diazo compound.

$$\begin{array}{ccccc} Me_2C:CH \cdot COMe & & Me_2C \cdot CH_2 \cdot COMe & & Me_2C \cdot CH_2 \cdot COMe \\ + & \longrightarrow & | & \longrightarrow & | \\ R \cdot CH_2 \cdot NH_2 & & R \cdot CH_2 \cdot NH & & R \cdot CH_2 \cdot N \cdot NO \end{array}$$

$$\longrightarrow Me_2C:CH \cdot COMe + R \cdot CHN_2 + H_2O$$
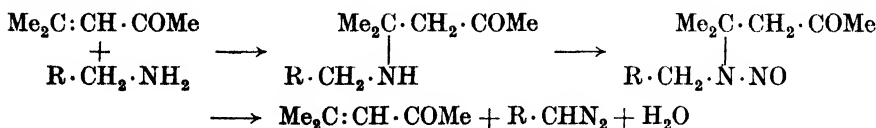
The method is the most general one known for the preparation of diazo

[1] *Annalen*, 1910, **376**, 252.

[2] E. C. S. Jones and J. Kenner, *J.C.S.* 1933, 363; D. W. Adamson and J. Kenner, ibid. **1935**, 286.

hydrocarbons, since practically any primary amine can be converted into the diazo derivative. The yield is not high from heptyl- and octyl-amine, and the reaction fails with cyclobutylamine and cyclobutylmethylamine; but even such a compound as vinyldiazomethane, $CH_2:CH \cdot CHN_2$, can be obtained by this method in 40 per cent. of the theoretical yield.

(2) Curtius's method[1] is of limited application. Whereas the majority of primary aliphatic amines react with nitrous acid to give nitrogen and an alcohol, $R \cdot NH_2 + ONOH \longrightarrow ROH + N_2 + H_2O$, a certain number in which there is a 'negative' group in the α-position to the amino group give an aliphatic diazo compound. The more important examples are esters of α-amino acids (but not the acids themselves), α-amino nitriles, as $NC \cdot CH_2 \cdot NH_2$, and compounds such as ω-amino-acetophenone,

$$\phi \cdot CO \cdot CH_2 \cdot NH_2.$$

Measurements of the rate of reaction of nitrous acid with amines, both of the class which gives no diazo compound and of that which does, show that the order of the reaction is the same in both;[2] in every case the reaction is of the third order and the rate is proportional to the concentrations of the amine kation, of the nitrite ion, and of undissociated nitrous acid. A reaction complex, $RNH_3^+ + NO_2^- + HNO_2$, seems to be formed which breaks up into the reaction products, together with an unchanged molecule of nitrous acid, whatever the reaction products may be. A diazo compound is formed only when there is a carbonyl, carbethoxy or nitrile group in the α-position, and it is these groups which increase the stability of the diazo compounds. Hence it has been suggested that a diazo compound is always formed in the first instance, and only survives when the necessary stabilizing group is present. Such an explanation is, however, improbable, because it is known that when an optically active amino compound whose centre of asymmetry is the carbon atom carrying the amino group is converted by nitrous acid into an alcohol, the alcohol is optically active. If the aliphatic diazo compound were an intermediate stage, this could not be the case, because it is known that the diazo compound $RR'CN_2$ does not contain a centre of asymmetry and cannot be optically active; hence its decomposition product must be a racemic substance. The following scheme seems much more likely.

$$
\begin{array}{c}
R' \\
| \\
R-C-NH_2 + ONOH \longrightarrow R-C-N{:}N\cdot OH \Big\langle \begin{array}{c} R-CN_2 + H_2O \\ \\ R-C-OH + N_2 \end{array} \\
| \\
H
\end{array}
$$
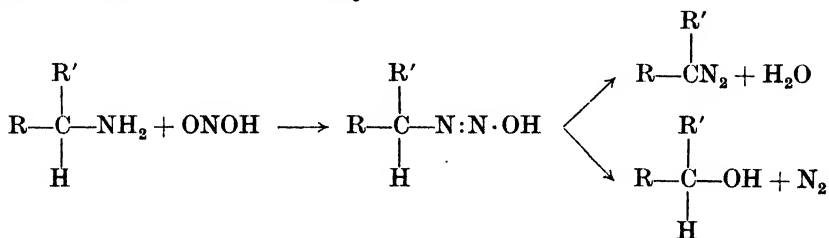
In this the intermediate compound is analogous to an aromatic diazo

[1] Ber. 1883, 16, 754.
[2] T. W. J. Taylor and L. S. Price, J.C.S. 1929, 2052.

compound and has two modes of decomposition; it may either lose nitrogen directly to give the alcohol, in which reaction the carbon atom can retain its asymmetry, or it may lose water to give an aliphatic diazo compound. For the second alternative to proceed the hydrogen atom which is eliminated with the hydroxyl group must be able to leave the carbon atom, and this may be the reason why a carbethoxy or carbonyl group in the α-position favours the formation of the aliphatic diazo compound, since these groups are known to make such a hydrogen atom mobile.

Diazoacetic ester is prepared by this method from glycine ester hydrochloride.

$$CH_2(NH_2)\cdot CO_2Et + ONOH \longrightarrow CHN_2\cdot CO_2Et + 2H_2O$$

The reaction is carried out by adding dilute sulphuric acid to an aqueous solution of equivalent quantities of the ester hydrochloride and sodium nitrite beneath a layer of ether. The ethereal layer is removed and replaced by fresh ether from time to time in order to preserve the diazo ester, which is dissolved in the ether, from contact with the mineral acid by which it is readily decomposed.

(3) The third method has a curious history. Curtius and his co-workers[1] investigated the oxidation of the hydrazones of aldehydes and ketones ($RR'C:N\cdot NH_2$) with yellow mercuric oxide. They concluded that with some hydrazones the product was a diazo compound, as with the monohydrazone of benzil, $\phi\cdot CO\cdot C\phi:N\cdot NH_2$, but that others, such as benzophenone hydrazone, $\phi_2C:N\cdot NH_2$, gave as product a compound containing a chain of four nitrogen atoms, a group of substances which they named tetrazones.

$$\phi\cdot C(:N\cdot NH_2)\cdot CO\cdot\phi \longrightarrow \phi\cdot CN_2\cdot CO\cdot\phi$$

$$2\phi_2C:N\cdot NH_2 \longrightarrow \phi_2C:N\cdot N:N\cdot N:C\phi_2$$
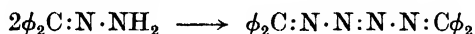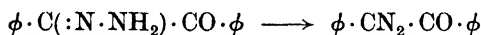
In 1910 M. O. Forster and A. Zimmerli[2] suggested that the tetrazones were non-existent and that in all cases the product was an aliphatic diazo compound. This was conclusively proved by H. Staudinger and O. Kupfer,[3] who showed that the 'tetrazones' have a molecular weight half as great as that demanded by Curtius's formula and that their reactions are identical with those of the aliphatic diazo compounds.

This method is of value for obtaining the diazo derivatives which contain aromatic hydrocarbon residues. Thus diphenyl-diazomethane, ϕ_2CN_2, can be prepared by shaking benzophenone hydrazone with yellow mercuric oxide in cold petroleum ether:[4] after 6–9 hours the mercury is removed and evaporation of the solvent leaves diphenyldiazomethane as dark red needles in a yield of 85–98 per cent. of the theoretical.

There are a few other methods whereby compounds of this class are formed. If chloroform and hydrazine react together in the presence of

[1] *J. pr. Chem.* 1891, **44**, 182, 200, 535.
[2] *J.C.S.* 1910, **97**, 2156. [3] *Ber.* 1911, **44**, 2197.
[4] H. Staudinger, E. Anthes, and F. Pfenninger, ibid. 1916, **49**, 1932.

alkali, diazomethane is formed;[1] the reaction probably proceeds in the normal way (see p. 317) with the production of the isocyanide, $NH_2 \cdot NC$, which rearranges to diazomethane. The yield is bad because some of the diazomethane reacts with the hydrazine to form methylhydrazine:

$$NH_2 \cdot NH_2 + CH_2N_2 \longrightarrow NH_2 \cdot NHCH_3 + N_2.$$
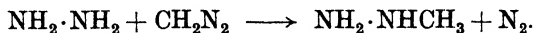
Finally it may be mentioned that certain hydroxytriazoles, which are stable as their alkali salts, change spontaneously, either totally or in part, into diazo derivatives of acid amides when set free from those salts. The extent to which the change takes place depends on the nature of the substituents R and R'. In some cases there is a true equilibrium between the two compounds and these tautomeric cases have been exhaustively

$$
\begin{array}{ccc}
& NR & \\
HOC & N & CO \cdot NHR \\
\| & \| & \rightleftharpoons \quad | \\
R' \cdot C {\rule{1cm}{0.4pt}} N & & R' \cdot CN_2
\end{array}
$$
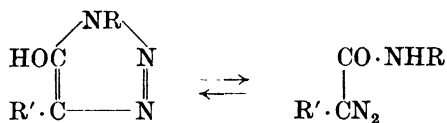
investigated by Dimroth and his school and were of great importance in the development of the subject of tautomerism.[2]

In physical properties and in stability to acids and to heat the aliphatic diazo compounds vary over a wide range. It may be said in general that those in which a hydrocarbon residue is united to the diazo group are highly coloured and comparatively unstable, while those containing one carbonyl group in the α-position to the diazo group are yellow and more stable, and those with two such groups are almost colourless and quite stable.[3] The contrast between the extremes is so great that the most stable class have sometimes been thought to have a different constitution and have been called 'diazo anhydrides': this point is discussed below (see p. 362).

Diazomethane itself is a deep yellow gas; it boils at $-23°$ and solidifies at $-145°$.[4] Higher members are yellow liquids, such as diazoacetic ester, boiling-point 46–47°/15 mm., 140°/720 mm., and phenyldiazomethane, boiling-point 81°/15 mm., or low-melting solids such as benzoyldiazomethane, melting-point 50°. Nearly all explode when heated rapidly to 100–150°. Diazomethane is a somewhat dangerous compound both in the liquid and gaseous states, sometimes exploding at quite low temperatures, especially when impure: its solutions, however, are much more stable. In the explosive decomposition of many of these compounds there is a marked emission of light, a phenomenon which has been investigated most closely in the case of diphenyldiazomethane.[5] The

[1] H. Staudinger and O. Kupfer, ibid. 1912, 45, 501.

[2] O. Dimroth, Annalen, 1904, 335, 1; 1905, 338, 143; 1909, 364, 197; 1910, 373, 336; 377, 127; 1913, 399, 91.

[3] A table showing this is given by H. Staudinger and Alice Gaule, Ber. 1916, 49, 1902.   [4] H. Staudinger and O. Kupfer, ibid. 1912, 45, 507.

[5] H. Staudinger, E. Anthes, and F. Pfenninger, ibid. 1916, 49, 1933.

moment before explosion takes place the substance is surrounded by a bluish glow which is little affected by the nature of the gas in the vessel containing the substance. Nitrogen is evolved in the decomposition but the glow is not due to the presence of active nitrogen, because if the explosion takes place in an atmosphere of acetylene or ethylene, no hydrogen cyanide can be detected among the products, whereas active nitrogen is known to give this compound with both of these gases.

The chemical properties of the aliphatic diazo compounds can be divided into three main classes.

1. *Reactions in which nitrogen is evolved.* When an aliphatic diazo compound is treated with a dilute aqueous acid, nitrogen is evolved and the elements of water are added on to give a hydroxy compound; thus diazoacetic ester gives glycollic ester:

$$CHN_2 \cdot CO_2Et \longrightarrow CH_2OH \cdot CO_2Et + N_2.$$
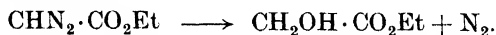
In alcoholic solution a similar reaction takes place with the production of an ethoxy compound.

$$CHN_2 \cdot CO_2Et \longrightarrow CH_2OEt \cdot CO_2Et$$
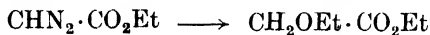
The velocity of these reactions can be easily followed by measuring the volume of nitrogen evolved; in dilute aqueous or alcoholic solution the reaction is unimolecular and during the initial stages the rate is proportional to the hydrogen-ion concentration.[1] If the acid is more concentrated, this reaction is accompanied by another in which a molecule of the acid itself combines additively; and thus the whole reaction gradually slows down because of the removal of the catalysing acid.

$$CHN_2 \cdot CO_2Et + HCl \longrightarrow CH_2Cl \cdot CO_2Et + N_2$$
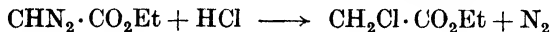
The concentration of acid at which this reaction becomes appreciable varies with the acid: hydriodic acid even when quite dilute gives iodoacetic ester with diazoacetic ester. This displacement of nitrogen by a molecule of the acid takes place very readily in solvents such as benzene, and under these conditions it is a reaction of the undissociated acid.[2]

A reaction similar to that with water takes place between aliphatic diazo compounds and most compounds containing a hydroxyl, amino or imino group, although with very varying ease. If diazomethane is used, methoxy or N-methyl compounds are formed and the reaction provides a valuable method of methylation. Alcohols do not react with diazomethane in the absence of an acid catalyst, but phenols react readily at room temperature, and the more acidic the phenol the more rapid the reaction. The enolic forms of substances such as acetoacetic ester also react with diazomethane, and this is the only way in which their methyl ethers, e.g. $CH_3 \cdot C(OMe){:}CH \cdot CO_2Et$, can be conveniently prepared. In the case of ortho-substituted phenols, the reaction does not proceed so readily, especi-

[1] G. Bredig and W. Fränkel, *Z. Elektrochem.* 1905, **11**, 525.

[2] Staudinger and Gaule, loc. cit.; A. Weissberger and J. Högen, *Z. phys. Chem.* 1931, A, **156**, 321; J. N. Brönsted and R. P. Bell, *J. Amer. C. S.* 1931, **53**, 2478.

ally if the substituent is an acyl or carbethoxy group: this may be pure steric hindrance, but is more probably connected with the interaction between the phenolic hydroxyl and the carbonyl groups which is described as chelation (see p. 269). Diazomethane in the presence of a little water can displace the acetyl group of an acetylated phenol:

$$\phi \cdot O \cdot CO \cdot CH_3 + CH_2N_2 + H_2O \longrightarrow \phi \cdot OCH_3 + N_2 + CH_3 \cdot CO_2H.$$

It has no action, however, on an acetylated amine,[1] and in the absence of ortho-substituents it can thus be used to distinguish between the O- and N-acetyl derivatives of amino-phenols.

Diazomethane does not react at all readily with primary amines in an anhydrous solvent, but in certain cases the reaction is vigorously catalysed by a small amount of water.[2] The acidic hydrogen atom of the cyclic imide of a dibasic acid, such as phthalimide, is rapidly attacked to give the N-methyl imide.[3]

Another example of the reactions of this class is that with the halogens: nitrogen is rapidly lost and a di-halogen compound formed. Thus diazo-methane and iodine in ethereal solution give methylene iodide:

$$CH_2N_2 + I_2 \longrightarrow CH_2I_2 + N_2.$$
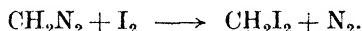
The reaction has been used for estimating the strength of ethereal solutions of diazomethane, but the results are always far too low;[4] a better method is based on the action of acids in non-dissociating solvents and consists of adding excess of an ethereal solution of benzoic or p-nitro-benzoic acid to the solution to be estimated, and determining the amount of acid left over by titration with baryta.[5] The reaction with the halogens has been used for showing the existence of bromine chloride, BrCl, in mixtures of bromine and chlorine and for estimating its concentration.[6] If an equimolecular mixture of bromine and chlorine in carbon tetra-chloride reacts with diazoacetic ester or benzoylphenyldiazomethane, $\phi \cdot CO \cdot CN_2 \cdot \phi$, a considerable proportion of the chlorobromo product is formed in addition to a certain amount of the dichloro and dibromo substances. In the case of benzoylphenyldiazomethane it is possible to analyse the reaction product and show that it contains 80 mol. per cent. of the chlorobromo compound: thus the proportion of BrCl in the mixture of bromine and chlorine is shown to be 80 per cent. in agreement with the spectroscopic measurements of L. T. M. Gray and D. W. G. Style.[7]

The two nitrogen atoms of the diazo group can be replaced by hydrogen atoms in many aliphatic diazo compounds by catalytic reduction with

[1] J. Herzig and J. Tichatschek, *Ber.* 1906, **39**, 268, 1557.
[2] H. Biltz and H. Paetzold, ibid. 1922, **55**, 1067.
[3] H. von Pechmann, ibid. 1895, **28**, 859.
[4] H. Staudinger and O. Kupfer, ibid. 1911, **44**, 505.
[5] E. K. Marshall and S. F. Acree, ibid. 1910, **43**, 2323.
[6] T. W. J. Taylor and L. A. Forscey, *J.C.S.* 1930, 2272.
[7] *Proc. Roy. Soc.* 1930, A, **126**, 603.

gaseous hydrogen in the presence of colloidal palladium; thus diazoacetic ester is quantitatively transformed into acetic ester at room temperature, gaseous nitrogen being evolved.[1] An interesting application of this reaction to the question of the alleged optical activity of aliphatic diazo compounds of the general formula $RR'CN_2$ was made by A. Weissberger and R. Haase.[2] They found that the rotation of an optically active sample of the diazo compound was unchanged by treating it with hydrogen and palladium; since this treatment converts the diazo compound into the molecule $RR'CH_2$ in which there is no centre of asymmetry, it follows that the observed activity is not due to the diazo compound, but to optically active impurities associated with it.

All aliphatic diazo compounds decompose on heating, many on standing at room temperature, and the decomposition is nearly always accompanied by loss of nitrogen as gas. The products are very varied, since the first stage of the decomposition is the methylene radical $RR'C{<}$, which, since it cannot exist as such for any length of time, gives a variety of secondary products. In the case of diazomethane the primary product is methylene itself and this has been detected by means of its reaction with tellurium.[3] If gaseous diazomethane is carried in a stream of ether vapour or butane at low pressure through a furnace at 500–550°, the emerging gases contain a substance which is able to attack tellurium at room temperature to give a red non-volatile solid of composition $(CH_2Te)_n$. The substance cannot be the methyl radical, which is well known to be a product of the decomposition of compounds such as lead tetramethyl, because the methyl radical gives with tellurium dimethyl ditelluride, $CH_3Te \cdot TeCH_3$, a red liquid, and also reacts with metallic zinc and lead. The decomposition product of diazomethane does not react with the two latter metals at all, and is clearly the methylene radical CH_2. It is, of course, quite unstable and has a half-life period of only a few thousandths of a second.

The products ordinarily obtained in the thermal decomposition of aliphatic diazo compounds can be classified as follows:

(*a*) The methylene radical combines with an undecomposed molecule of diazo compound to give an azine. If a solution of phenyldiazomethane in benzene is warmed, a copious precipitate of benzal-azine forms, identical with the compound obtained from the interaction of two molecules of benzaldehyde with one of hydrazine.

$$\phi CH{<} + \phi CHN_2 \longrightarrow \phi CH{:}N{\cdot}N{:}CH\phi \longleftarrow \phi CHO + H_2N{\cdot}NH_2 + OCH\phi$$
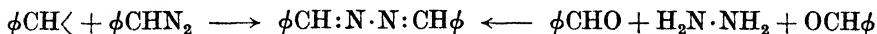
(*b*) The methylene radical polymerizes to an ethylene compound. The reaction is often catalysed by copper powder[4] or by anhydrous copper

[1] H. Wienhaus and H. Ziehl, *Ber.* 1932, **65**, 1461; H. Staudinger, ibid. 1916, **49**, 1896.

[2] Ibid. 1931, **64**, 2899; A. Weissberger, R. Haase, and H. Bach, ibid. 1932, **65**, 265.

[3] F. O. Rice and A. L. Glazebrook, *J. Amer. C. S.* 1934, **56**, 2381.

[4] A. Loose, *J. pr. Chem.* 1909, **79**, 507.

sulphate.[1] Thus diazoacetic ester with copper powder in boiling ligroin gives fumaric ester, and phenyldiazomethane heated in the absence of a solvent gives stilbene.

$$2\,EtO_2C\cdot CH\langle \longrightarrow \begin{array}{c} HC\cdot CO_2Et \\ \| \\ EtO_2C\cdot CH \end{array} \qquad 2\,\phi CH\langle \longrightarrow \begin{array}{c} H\cdot C\cdot\phi \\ \| \\ \phi\cdot C\cdot H \end{array}$$
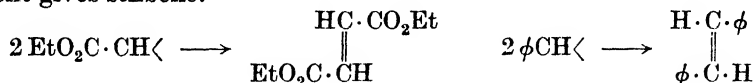
The ethylenic compound can itself react with the diazo compound, as is discussed below, and thus a pyrazoline derivative is often formed as well.

(c) The methylene radical may undergo rearrangement. An example is G. Schroeter's observation[2] that benzoylphenyldiazomethane, if warmed to 50° in benzene solution in a stream of carbon dioxide, is converted into diphenyl ketene.

$$\begin{array}{c} \phi \\ \diagdown \\ \phi\cdot CO \end{array}\!\!\!\!\diagup CN_2 \longrightarrow \begin{array}{c} \phi \\ \diagdown \\ \phi\cdot CO \end{array}\!\!\!\!\diagup C\langle \longrightarrow \begin{array}{c} \phi \\ \diagdown \\ \phi \end{array}\!\!\!\!\diagup C{=}C{=}O$$
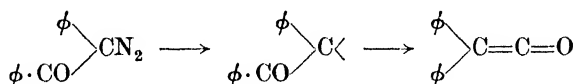
Since this diazo compound is easily obtained from benzil by oxidation of its monohydrazone with mercuric oxide, this reaction renders diphenyl ketene one of the most easily prepared ketenes.

(d) If oxygen is present, the methylene radical is sometimes oxidized to a ketone:[3] $\phi_2C\langle \longrightarrow \phi_2CO$.

2. *Reactions in which nitrogen is not lost.* The most important example is reduction. The products of reduction vary with the reducing agent used, but the first product that can be isolated is a hydrazone of the structure $RR'C:N\cdot NH_2$: this is the product obtained by the action of hydrogen sulphide on diazoacetic ester[4] and of hydrogen in the presence of colloidal palladium on diazomalonic ester, $N_2C(CO_2Et)_2$. With other reducing agents the reduction products of the hydrazone are obtained: thus sodium amalgam reduces diazomethane to methylhydrazine, $MeNH\cdot NH_2$, and zinc dust and acetic acid reduce diazoacetic ester to ammonia and the amino-acid glycine.[5] The constitution of the primary reduction product, $RR'CN_2H_2$, is of some importance from the point of view of the constitution of the diazo compounds themselves. At one time it was thought that they were not hydrazones, $RR'C:N\cdot NH_2$, but hydrazi compounds, $RR'C\!\!\diagup\!\!\begin{array}{c}NH \\ | \\ NH'\end{array}$,

which, if true, would indicate a cyclic structure for the diazo compounds. They are, however, hydrazones and of the many facts pointing to this conclusion[6] the following observations of Staudinger are perhaps the most interesting. If diazomalonic ester is reduced, there is one product, the

[1] K. Lorey, *ibid.* 1930, **124**, 185.

[2] *Ber.* 1909, **42**, 2345.

[3] H. Staudinger, E. Anthes, and F. Pfenninger, *Ber.* 1916, **49**, 1935.

[4] O. Dimroth, *Annalen*, 1910, **373**, 338; O. Piloty and J. Neresheimer, *Ber.* 1906, **39**, 516; H. Staudinger, J. Siegwart, and A. Gaule, *Helv. Chim. Acta*, 1921, **4**, 212.

[5] See also A. Darapsky and M. Prabhakar, *Ber.* 1912, **45**, 1654.

[6] See e.g. E. Müller, *ibid.* 1914, **47**, 3005.

hydrazone of mesoxalic ester, which can be hydrolysed to that ester and hydrazine.

$$(EtO_2C)_2C{:}N{\cdot}NH_2 \longrightarrow (EtO_2C)_2CO + H_2N{\cdot}NH_2$$
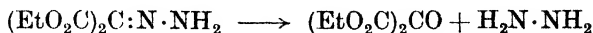
If, however, diazoacetic ester is reduced, the initial product, a comparatively unreactive liquid insoluble in water, changes on standing or warming to the extent of two-thirds into an isomer melting at 38·5° and soluble in water. Both these substances can be hydrolysed to hydrazine and glyoxylic ester, and are readily interconvertible: they can be separated by distillation, their boiling-points being 40° and 105–106°/0·2 mm. The two compounds must be geometrical isomers, the isomerism arising from the presence of the grouping $\rangle C{=}N{-}$, as in certain oximes. This view will explain the appearance of isomerism in the reduction products of diazoacetic ester and not in the case of diazomalonic ester, because in the latter compound the two groups attached to the carbon atom are identical and geometrical isomerism cannot occur. Their structures must be:

$$\begin{array}{cc} H{\cdot}C{\cdot}CO_2Et & H{\cdot}C{\cdot}CO_2Et \\ \| & \| \\ N{\cdot}NH_2 & H_2N{\cdot}N \end{array}$$

The great difference in volatility between these two isomers is exactly paralleled by that between the geometrically isomeric phenylhydrazones of acetaldehyde (see p. 397). The fact that these compounds are geometrically isomeric makes the cyclic hydrazi structure very improbable: such isomerism could only be accounted for with a cyclic structure by assuming that there was *cis-trans* isomerism about the ring in which the hydrogen atoms attached to the saturated trivalent nitrogen atoms are involved. No such isomerism has ever been observed when trivalent nitrogen is concerned, and the case would be unique (see p. 39).

Another example of a reaction of diazomethane in which nitrogen is not eliminated is that with the chloride of a carboxylic acid,[1] but the nature of the product obtained depends upon the conditions under which the reaction is carried out. The first product is a diazo-ketone formed by elimination of hydrogen chloride between the acid chloride and diazomethane.

$$RCO{\cdot}Cl + CH_2N_2 \longrightarrow R{\cdot}CO{\cdot}CHN_2 + HCl$$
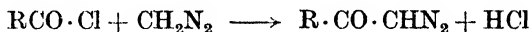
The diazo-ketone is, of course, liable to decomposition by the hydrogen chloride, but if diazomethane is in excess this is attacked preferentially, $CH_2N_2 + HCl \longrightarrow CH_3Cl + N_2$, and the diazo-ketone can be obtained in good yield. Otherwise the diazo-ketone is attacked and the chloroketone formed. Hence the product obtained often depends on whether the chloride is added to the diazomethane solution or vice versa.

3. *Additions to unsaturated compounds.* In most cases aliphatic diazo compounds will add on to an ethylenic or acetylenic link to give a pyrazoline or pyrazole derivative.

[1] F. Arndt and J. Amende, *Ber.* 1928, **61**, 1122.

$$\underset{R'}{\overset{R}{\diagdown}}CN_2 + \rangle C = C \langle \longrightarrow \underset{R'}{\overset{R}{\diagdown}} \begin{matrix} C - N \\ | \quad \diagdown N \\ C - C \\ \wedge \end{matrix}$$

$$\underset{R'}{\overset{R}{\diagdown}}CN_2 + -C \equiv C- \longrightarrow \underset{R'}{\overset{R}{\diagdown}} \begin{matrix} C - N \\ | \quad \diagdown N \\ -C = C \\ | \end{matrix}$$
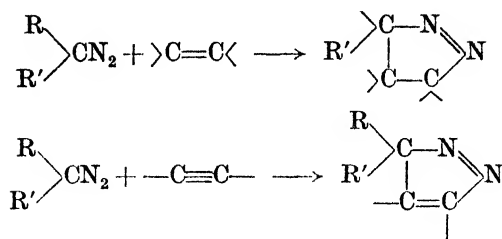
Thus diazomethane reacts with acetylene to give a 50 per cent. yield of pyrazole and less easily with ethylene to give pyrazoline.[1] Vinyldiazomethane contains an ethylenic double bond and a diazo group in the same molecule, so that intramolecular addition can take place. The deeply coloured ethereal solution of vinyldiazomethane slowly loses its colour on standing at room temperature, and in a few minutes at the boiling-point of ether, and pyrazole (IV) is formed; the reaction is unimolecular.[2]

$$CH_2:CH \cdot CHN_2 \longrightarrow \begin{matrix} CH - CH \\ \| \qquad \| \\ N \quad CH \\ \diagdown \diagup \\ NH \end{matrix}$$

IV.
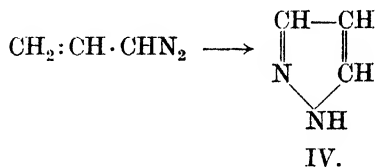
Addition of aliphatic diazo compounds to $\alpha\beta$-unsaturated esters takes place very readily: fumaric ester and diazoacetic ester give pyrazoline 3,4,5-tricarboxylic ester, and hence this compound is found among the decomposition products of diazoacetic ester on warming,[3] since, as we have already seen, fumaric ester is formed in the decomposition. If the pyrazoline carboxylic esters are heated, they lose nitrogen and are converted into cyclopropane derivatives. The reaction recalls the behaviour of

$$\begin{matrix} EtO_2C \cdot CH —— N \\ | \qquad\qquad \diagdown N \\ EtO_2C \cdot CH — CH_2 \diagup \end{matrix} \longrightarrow \begin{matrix} EtO_2C \cdot CH \\ | \qquad\qquad \diagdown CH_2 + N_2 \\ EtO_2C \cdot CH \diagup \end{matrix}$$
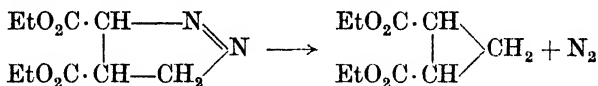
certain aliphatic azo compounds (see p. 432). An interesting example of this reaction is that between diazoacetic ester and benzene, which was exhaustively investigated by Buchner and his pupils. If diazoacetic ester is heated with a large excess of benzene, nitrogen is evolved and a compound is formed which is isomeric with phenylacetic ester, and hence called pseudo-phenylacetic ester. The corresponding acid is unsaturated and forms a tetrabromide by addition: it thus contains two double bonds. It is oxidized by permanganate to cyclopropane 1,2,3-tricarboxylic acid, and thus contains a three-membered ring. Its structure is thus established as (V), and its formation is exactly similar to the normal reaction with an

[1] H. v. Pechmann, ibid. 1898, **31**, 2950.

[2] D. W. Adamson and J. Kenner, *J.C.S.* 1935, 288.

[3] O. Silberrad and C. S. Roy, ibid. 1906, **89**, 179.

ethylenic compound, the pyrazoline having lost nitrogen. This is one of the few reactions in which benzene behaves as an ethylenic compound.

$$\text{V.} \qquad \begin{array}{c} \text{CH} \\ \text{CH} \quad \text{CH} \\ \text{CH} \quad \text{CH} \\ \text{CH} \end{array} \hspace{-0.5em} \text{CH} \cdot \text{CO}_2\text{H}$$
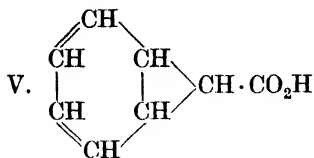
Diazoacetic ester will react with malonic ester and cyanacetic ester in presence of alkaline condensing agents such as caustic soda or sodium ethoxide. The product is a 4-hydroxy- or 4-amino-pyrazole dicarboxylic ester, and seems to be formed by addition of the diazo compound to the double bond of the enolic form of the ester.[1]

$$\begin{array}{c} \text{EtO}_2\text{C} \cdot \text{CH} \\ \| \\ \text{HO} \cdot \text{C} \cdot \text{OEt} \end{array} + \text{N}_2\text{CH} \cdot \text{CO}_2\text{Et} \longrightarrow \begin{array}{c} \text{NH} \\ \text{EtO}_2\text{C} \cdot \text{C} \qquad \text{N} \\ \| \qquad\qquad \| \\ \text{HO} \cdot \text{C} \text{———} \text{C} \cdot \text{CO}_2\text{Et} \end{array}$$

$$\begin{array}{c} \text{EtO}_2\text{C} \cdot \text{CH} \\ \| \\ \text{C} \\ \| \\ \text{NH} \end{array} + \text{N}_2\text{CH} \cdot \text{CO}_2\text{Et} \longrightarrow \begin{array}{c} \text{NH} \\ \text{EtO}_2\text{C} \cdot \text{C} \qquad \text{N} \\ \| \qquad\qquad \| \\ \text{H}_2\text{N} \cdot \text{C} \text{———} \text{C} \cdot \text{CO}_2\text{Et} \end{array}$$
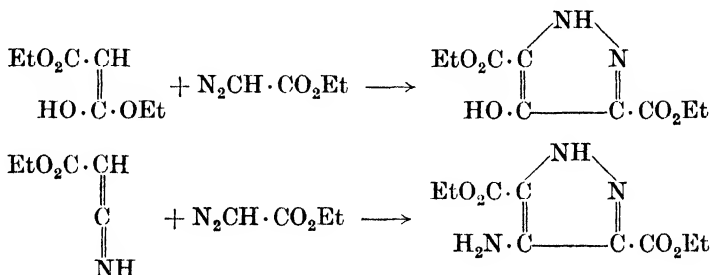
Aliphatic diazo compounds can also add on to the double bond between nitrogen atoms in the azo group. The addition proceeds much in the same way as with ethylenic compounds, but the intermediate stage, which in this case would be a tetrazoline with four hetero-atoms, cannot be isolated; nitrogen is lost at once and a hydrazi compound is formed. Thus diazoacetic ester reacts with azodicarboxylic ester[2] in ethereal solution at room temperature with loss of nitrogen.

$$\begin{array}{c} \text{EtO}_2\text{C} \cdot \text{N} \\ \| \\ \text{EtO}_2\text{C} \cdot \text{N} \end{array} + \text{CHN}_2 \cdot \text{CO}_2\text{Et} \longrightarrow \begin{array}{c} \text{EtO}_2\text{C} \cdot \text{N} \\ \quad | \quad \hspace{-0.5em}\rangle \text{CH} \cdot \text{CO}_2\text{Et} + \text{N}_2 \\ \text{EtO}_2\text{C} \cdot \text{N} \end{array}$$
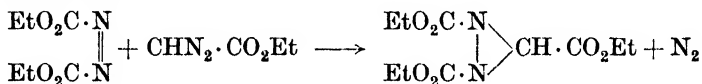
This is one of the few reactions whereby true hydrazi compounds have been obtained: they rearrange, often quite easily, into hydrazones,

$$\text{R}_2\text{N} \colon \text{N} \colon \text{CH} \cdot \text{R}'.$$
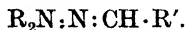
Addition of diazomethane to the carbonyl group can lead to a variety of products; the course of the reaction has been carefully studied by F. Arndt and his pupils.[3] They have shown that the formation of the various products can be best accounted for by making the very probable assumption that addition of diazomethane to the double bond takes place as in the ethylenic compounds, and is followed by loss of nitrogen to give a radical which can rearrange in several different ways. Aldehydes

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[1] A. Bertho and H. Nüssell, *Annalen,* 1927, **457**, 278.
[2] E. Müller, *Ber.* 1914, **47**, 3001.   [3] e.g. ibid. 1928, **61**, 1118; 1929, **62**, 44.

contain a reactive carbonyl group and react readily: in many cases the product is the methyl ketone (VI), but in others it is almost entirely the ethylene oxide (VII).

$$\begin{array}{c} R \\ H \end{array}\!\!\Big\rangle C{=}O + CH_2N_2 \longrightarrow \begin{array}{c} R \\ H \end{array}\!\!\Big\rangle C\!\!\Big\langle \begin{array}{c} O\!-\!-\!N \\ \| \\ CH_2\!-\!N \end{array}$$

$$\longrightarrow \begin{array}{c} R \\ H \end{array}\!\!\Big\rangle C\!\!\Big\langle \begin{array}{c} O\!- \\ CH_2\!- \end{array} \Bigg\langle \begin{array}{c} \nearrow \quad R\cdot CO\cdot CH_3 \qquad VI. \\ \\ \searrow \quad R\cdot \underset{O}{\underset{\diagdown\diagup}{CH\!-\!CH_2}} \quad VII. \end{array}$$
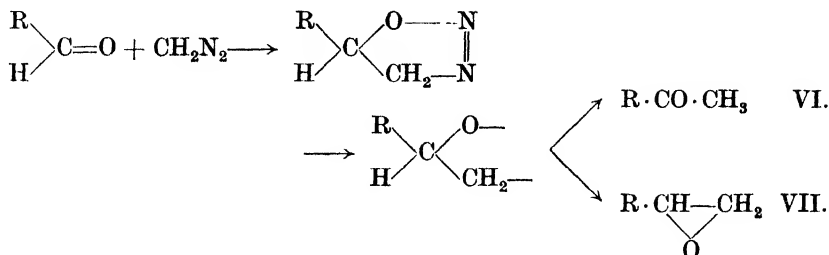
That an actual addition compound is first formed without loss of nitrogen is well shown in the case of chloral; this appears to combine with diazomethane in ethereal solution, but no nitrogen is evolved until the ether is removed under reduced pressure. Water and the simple alcohols catalyse the decomposition of the addition complex, so that if chloral hydrate is used instead of chloral, nitrogen is evolved immediately its ethereal solution is added to one of diazomethane. Whether ketone or ethylene oxide is formed is determined by the nature of the aldehyde; those, like chloral, which unite with water or form acetals very readily give almost entirely the ethylene oxide. The carbonyl group of a ketone is less reactive and the ketones do not in general react with diazomethane except in the presence of a catalyst such as water.[1] Under those conditions the reaction takes a course similar to that with the aldehydes: acetone is converted in the presence of alcohols partly into dimethylethylene oxide and partly, by the wandering of a methyl group, into methylethyl ketone:

$$\begin{array}{c} CH_3 \\ CH_3 \end{array}\!\!\Big\rangle CO + CH_2N_2 \longrightarrow N_2 + \begin{array}{c} CH_3 \\ CH_3 \end{array}\!\!\Big\rangle C\!\!\Big\langle \begin{array}{c} CH_2\!- \\ O\!- \end{array} \Bigg\langle \begin{array}{c} \nearrow \quad \underset{O}{\underset{\diagdown\diagup}{Me_2C\!-\!CH_2}} \\ \\ \searrow \quad CH_3\cdot CO\cdot CH_2\cdot CH_3. \end{array}$$
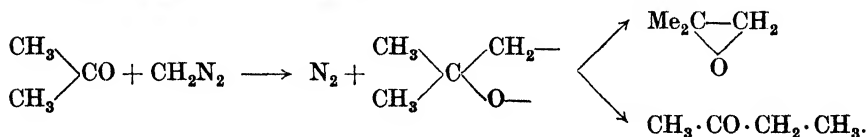
The formation of the two products recalls the action of dehydrating agents on a glycol, when either the ethylene oxide may be formed or else rearrangement may take place to a ketone:

$$\begin{array}{c} R_2C\!-\!CR_2 \\ |\quad\; | \\ OH\; OH \end{array} - H_2O \Bigg\langle \begin{array}{c} \nearrow \quad \underset{O}{\underset{\diagdown\diagup}{R_2C\!-\!CR_2}} \\ \\ \searrow \quad R_3C\cdot CO\cdot R. \end{array}$$
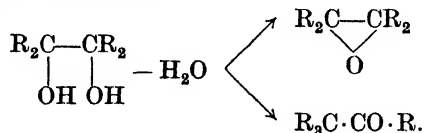
If cyclic ketones are used, the rearrangement of the intermediate radical often takes place with enlargement of the ring, as was first observed by G. Heller.[2] Cyclohexanone, for example, reacts with diazomethane in ether in the presence of anhydrous methyl alcohol to give a mixture of the ethylene oxide, cycloheptanone and cyclo-octanone, the latter presumably

[1] H. Meerwein and W. Burneleit, ibid. 1928, **61**, 1840.   [2] Ibid. 1919, **52**, 741.

coming from a further reaction of the cycloheptanone.[1] Similarly isatin gives an ethylene oxide and also 2,3-dihydroxyquinoline.
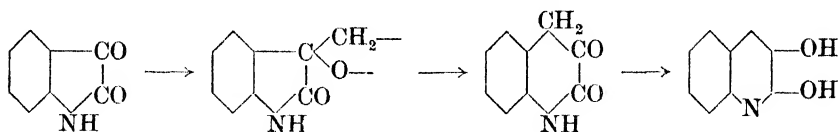
The Structure of the Aliphatic Diazo Group.

The constitution of the characteristic group, $:CN_2$, of the aliphatic diazo compounds was a matter of dispute for many years. The position was a somewhat curious one; there were two competing formulae, and a certain amount of evidence could be advanced in favour of both, although they implied two fundamentally different types of linkage of the constituent atoms of the group. The structure of the closely related azide group presented exactly the same problem, with two similar competing formulae. The position was further complicated for a time by the claims that were made that certain aliphatic diazo compounds of the general formula $RR'CN_2$ could be obtained in optically active forms. Since neither of the competing formulae could account for enantiomorphism, these claims did not clarify the position. However, Weissberger and his co-workers[2] succeeded in showing that these observations were erroneous and that the optical activity came from impurities present in the diazo compounds; hence this difficulty was removed (see p. 354).

The first structure to be proposed was that of a three-membered ring, $\rangle C\langle \begin{smallmatrix} N \\ \| \\ N \end{smallmatrix}$; this was put forward by Curtius and was universally accepted for many years. A curious feature is that the reasons which led him to the proposal are now known to be quite unsound. As has been mentioned already, his experiments had led him to believe that some hydrazones could be oxidized to 'tetrazones', while others gave diazo compounds. Since he attributed a chain of four nitrogen atoms to the 'tetrazones', he considered that their related hydrazones must have the structure
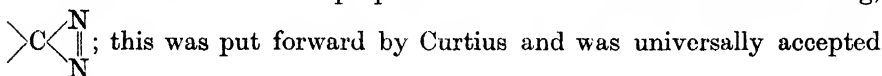
$$\rangle C:N\cdot NH_2.$$
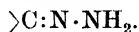
For the other class of hydrazones which on his view did not give 'tetrazones' on oxidation, he had no alternative but to propose the hydrazi structure $\rangle C\langle \begin{smallmatrix} NH \\ | \\ NH \end{smallmatrix}$, and this necessarily led to the above cyclic formula for their oxidation products, the aliphatic diazo compounds. We know now that tetrazones are non-existent and are in fact diazo compounds: there is no need to divide the hydrazones into two classes nor to assign to any of them a ring structure; they are, in fact, all straight chain compounds. Thus the original argument of Curtius has disappeared. Nevertheless, the

[1] E. Mosettig and A. Burger, *J. Amer. C. S.* 1930, **52**, 3456.

[2] *Ber.* 1931, **64**, 2896; 1932, **65**, 265; 1933, **66**, 559.

cyclic formula does express satisfactorily many of the reactions of the group. Three-membered rings such as ethylene imine and cyclopropane behave in some ways like unsaturated compounds, the ring opening with formation of addition products, so that the third class of reactions discussed above (p. 356) receives some explanation. The ring must be supposed to open between nitrogen and carbon and not between the nitrogen atoms, but, in view of the great stability of the $\cdot N:N\cdot$ link, this is not surprising.

When it was realized that all hydrazones were chain compounds, it seemed reasonable to assign a chain structure to the diazo compounds as well. A. Angeli[1] was the first to suggest the formula $>C=N=N$ and its claims were clearly put forward by J. Thiele in 1911.[2] The Angeli-Thiele formula seemed to represent the reactions of the group quite as satisfactorily as the cyclic formula, and indeed showed more clearly the relation between the diazo compound and its reduction product, the hydrazone, $>C:N:N \longrightarrow >C:N\cdot NH_2$. Written in this way, however, the formula contains a pentacovalent nitrogen atom; in other words it implies that the central nitrogen atom has a valency group of ten electrons. Such a state of combination is extremely improbable for reasons given elsewhere in this book (see especially p. 32); there is no organic compound of nitrogen known in which such a state occurs. Hence in its original form the Angeli-Thiele formula could not be accepted. It could be modified in two ways; the formula could be written either as $>C=N\rightarrow N$ or as $>C\leftarrow N\equiv N$. The chemical evidence was so scanty that it could not decide whether one of these formulae or the cyclic formula of Curtius was correct. The great majority of the reactions of the aliphatic diazo compounds involve the loss of the two nitrogen atoms and are consequently of little use for showing how they are linked in the molecule.

One piece of physical evidence, however, makes it impossible for either of the two straight chain formulae alone to be accepted; they both imply that the group should have a large electric moment in virtue of the co-ordinate link (semi-polar double bond) which each contains. The moment of the group has been measured,[3] and is of the order of only 1·4 D. For this and similar reasons the straight chain formula was rejected by many. The realization of the phenomenon of resonance altered the whole position. The two alternative straight chain formulae differ only in the distribution of their electrons, hence there is no true distinction between them, and the aliphatic diazo group may well be a resonance-hybrid of the two formulae. If this is so, the argument from electric moments will not apply, since the molecule has neither of two separate structures, and the formula is satisfactory from the point of view of both the chemical evidence and general valency theory.

Thus the real decision was between the cyclic formula and the resonance-hybrid straight chain formula. The actual position of the atoms in the

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[1] *Atti R.* 1907, **16**, ii, 790. [2] *Ber.* **44**, 2522.

[3] N. V. Sidgwick, L. E. Sutton, and W. Thomas, *J.C.S.* 1933, 406.

molecule of diazomethane has been established by measurements of electron diffraction,[1] and they show beyond any doubt that the straight chain is correct. The space arrangement of the molecule is shown in the following formula, in which the numbers are the distances found between the atoms in Ångström units.

$$\begin{matrix} \text{H} \\ \quad\quad \text{C } 1{\cdot}34{\pm}0{\cdot}05 \text{ N } 1{\cdot}13{\pm}0{\cdot}04 \text{ N} \\ \text{H} \end{matrix}$$
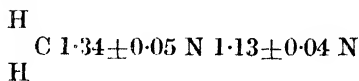
This result finds ample confirmation in what has been established for the azide group. As we shall see, evidence from three sources, electron diffraction, crystal structure, and heats of formation, is unanimous in showing that the azide group is a resonance-hybrid in which the atoms are arranged in a straight chain.

We may thus conclude that the aliphatic diazo group can only be represented as a resonance-hybrid of the two structures

$$\text{>C=N}{\rightleftharpoons}\text{N} \quad \text{and} \quad \text{>C}{\leftarrow}\text{N}{\equiv}\text{N}.$$
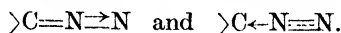
It is one of the few groups of organic chemistry for which no one formula can be written, even as an approximation.

A further point remains for discussion—the constitution of the so-called diazo anhydrides. This class consists of the acyl derivatives of diazo-acetic ester, $R \cdot CO \cdot CN_2 \cdot CO_2Et$, and the diazo derivatives of β-diketones, $R \cdot CO \cdot CN_2 \cdot CO \cdot R'$. The former can be obtained by the action of acyl chlorides on diazoacetic ester[2] which is similar to their action on diazo-methane itself (see p. 356): the latter were prepared by L. Wolff[3] by the action of nitrous acid on the amines obtained by reduction of the oximino compounds of β-diketones.

$$\cdot CO \cdot CH_2 \cdot CO \cdot \longrightarrow \cdot CO \cdot C({:}NOH) \cdot CO \cdot \longrightarrow \cdot CO \cdot CHNH_2 \cdot CO \cdot$$
$$\longrightarrow \cdot CO \cdot CN_2 \cdot CO \cdot$$
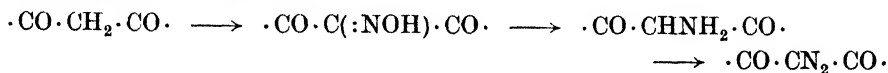
The diazo anhydrides are far less reactive than the other diazo compounds in every way, and much more stable to heat and acids. In general they show the same reactions, but in one particular they behave quite differently. Typical aliphatic diazo compounds are reduced by hydrogen sulphide to hydrazones or to the further reduction products of these, but diazo anhydrides give thiodiazoles which contain a five-membered ring.

$$R \cdot CO \cdot CN_2 \cdot CO \cdot R' \longrightarrow \begin{matrix} R' \cdot CO \cdot C{-}N \\ \| \quad\quad\quad \text{>N} \\ R \cdot C{-}S \end{matrix} \quad \text{VIII.} \quad \begin{matrix} R' \cdot CO \cdot C{-}N \\ \| \quad\quad\quad \text{>N} \\ R \cdot C{-}O \end{matrix}$$
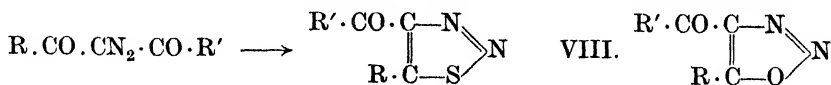
Because of this reaction Wolff allotted to the diazo anhydrides a constitution different from that of the true diazo compounds. He considered them to be furodiazoles (VIII). Staudinger has shown that this conclusion is difficult to maintain. He found that a diazo-anhydride is decomposed by

[1] H. Boersch, *Sitz. Akad. Wiss. Wien*, 1935, II b, **144**, 21; *Monats.* 1935, **65**, 331.

[2] H. Staudinger, J. Becker, and H. Hirzel, *Ber.* 1916, **49**, 1978.

[3] *Annalen*, 1903, **325**, 129.

the action of sodium ethoxide in a way which is identical with that which Dieckmann found for all di-substituted β-ketonic esters.

$$R \cdot CO \cdot CN_2 \cdot CO_2Et \longrightarrow R \cdot CO_2Et + CHN_2 \cdot CO_2Et$$

$$CH_3 \cdot CO \cdot CMe_2 \cdot CO_2Et \longrightarrow CH_3 \cdot CO_2Et + CHMe_2 \cdot CO_2Et$$
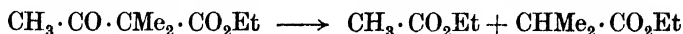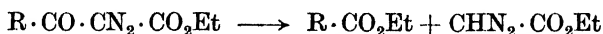
Further, if we take a diazo-anhydride derived from an unsymmetrical diketone, the action of hydrogen sulphide gives two isomeric thiodiazoles, because the ring can close with either of the two carbonyl groups.[1]
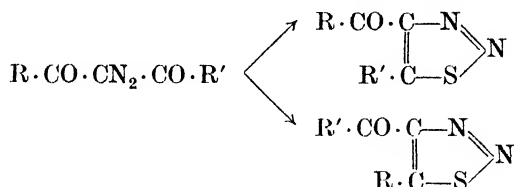
A diazo-anhydride, however, only exists as one substance and not as two isomers. The cyclic structure thus appears improbable. The diazo-anhydrides seem to be true aliphatic diazo compounds in which the stability is great and the reactivity small, because of the effect of the neighbouring carbonyl groups.

DERIVATIVES OF HYDRAZOIC ACID

The organic derivatives of hydrazoic acid can be divided into two classes: (i) the alkyl and aryl derivatives such as methyl azide, $CH_3 \cdot N_3$, and phenyl azide, $\phi \cdot N_3$, (ii) the acyl derivatives such as acetyl azide,

$$CH_3 \cdot CO \cdot N_3.$$
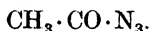
The structure of the azide group $-N_3$ will be discussed first, and then the two classes of derivatives will be described.

As already mentioned, the problem of the structure of the azide group is closely related to that of the aliphatic diazo group $>CN_2$. The azide group is monovalent and in many ways closely resembles the divalent diazo group; the former can be regarded as derived from the latter by the replacement of a tetravalent carbon atom by a trivalent nitrogen atom, the valency of the group consequently falling from two to one. This has long been realized and the structures of the two groups have always been discussed together and undergone modifications together. Thus the story of the structure of the azide group is largely a repetition of what has been said above about the diazo group. The first formula proposed by E. Fischer[2] was the cyclic one, $-N\overset{N}{\underset{N}{<}}\|$, and this was accepted until Angeli and Thiele suggested a straight chain structure $-N{=}N{\equiv}N$. There was the

[1] O. Dimroth, ibid. 1910, **373**, 339; H. Staudinger, *Helv. Chim. Acta*, 1921, **4**, 239.   [2] *Annalen*, 1878, **190**, 67.

same difficulty in deciding between these two formulae on the ground of chemical reactions, and the same confusion in the interpretations that could be placed on some of the physical properties. The solution of the problem and the demonstration that the cyclic formula is incorrect was reached when methods became available whereby the actual positions of the atoms in the molecule could be determined.

The structure of the azide ion N_3^-, as in potassium azide, was established by S. B. Hendricks and L. Pauling[1] by the complete X-ray analysis of sodium and potassium azides, and their results are confirmed by the Raman spectrum shown by the ion in solution.[2] The three nitrogen atoms lie in a straight line and the ion is symmetrical about the central nitrogen atom; its formula must be written $N\rightleftarrows\bar{N}\Rightarrow N$, or with dots representing electrons, $:\!\dot{N}\!:\!N\!:\!\dot{N}\!:$. The structure of the potassium azide crystal is almost identical with that of potassium cyanate which contains the ion $\bar{N}=C=O$ or $:\!\dot{N}\!:\!C\!:\!\dot{O}\!:$. The azide ion can be readily converted into an azide group which is covalently attached to a carbon atom and vice versa; the group N_3 behaves in many ways like chlorine which can exist both as an ion and as a covalently linked atom, and it is sometimes referred to as a pseudo-halogen. It seems unlikely that the transition from the ionized to the un-ionized state of combination involves any such profound alteration in structure as a change from a straight chain to a ring, especially in view of the large ring strain that the cyclic structure would probably possess. Yet there is no simple satisfactory way in which the azide group can be formulated as a chain covalently linked at one end. The formula suggested by Angeli and Thiele, $R{-}N{=}N{\equiv}N$, implies a pentacovalent nitrogen atom, a state of combination which seems to occur in no other compound of nitrogen. This formula can be emended to $-N{=}N\Rightarrow N$ or to $-N{\leftarrow}N{\equiv}N$, but either of these suggests that a compound like phenyl azide should show the large electric moment usually associated with a co-ordinate link, while the moment of phenyl azide is only $1\cdot55\,D$.[3]

The evidence for such a structure is, however, conclusive. Using the method of electron diffraction, L. O. Brockway and L. Pauling[4] determined the positions of the atoms in methyl azide and the distances between them; the molecule can be represented as shown, the figures indicating distances in Ångström units.

$$\text{N } 1\cdot26 \text{ N } 1\cdot10 \text{ N}$$
$$^{1\cdot47}$$
$$H_3C$$

[1] *J. Amer. C. S.* 1925, **47**, 2904.

[2] A. Langseth and J. R. Nielsen, *Phys. Review*, 1933, **44**, 326.

[3] E. Bergmann and W. Schütz, *Nature*, 1931, **128**, 1077; N. V. Sidgwick, L. E. Sutton, and W. Thomas, *J.C.S.* 1933, 408.

[4] *Proc. Nat. Acad. Sci.* 1933, **19**, 860.

This result was confirmed by the X-ray analysis of the crystals of cyanuric triazide, a compound of the formula

This has been carried out by two separate observers,[1] and both find the straight chain arrangement of the nitrogen atoms of the azide group, with practically the same distances between those atoms as was found by Brockway and Pauling. The only explanation that will account for all the facts is, as with the aliphatic diazo compounds, that there is no one simple formula for the azide group, but the structure is a resonance-hybrid between the two possible straight chain structures $R-N=N\overset{+}{\rightarrow}\overset{-}{N}$ and $R-N\leftarrow N\equiv N$, or, as Pauling would write them, $R:\overset{+}{N}::\overset{-}{N}:\overset{..}{N}:$ and $R:\overset{-}{\overset{..}{N}}:\overset{+}{N}:::N:$. It will be noticed that on this view the small value of the electric moment of the azide group is accounted for by the fact that the two structures from which the hybrid is derived have the moments of their co-ordinate links in opposite directions: also that the distances between the nitrogen atoms, which were found to be unequal, have values which are reasonable on the resonance-hybrid view: the shorter distance is between atoms which are linked by a bond which is a hybrid between a double and a treble bond, and the longer between atoms linked by a hybrid between a single and a double bond. This conclusion is upheld by the heat of formation of the azide, which is known to be 205–208 kg. cals. from the measurements of the heat of combustion of phenylazide and ethyl azido-acetate.[2] If as an approximation it is taken that the heats of formation are made up additively of contributions from each link in the group, it is possible to evaluate the heat of formation of the three alternative azide structures, the ring and the two straight chains.[3] The value for the ring cannot be greater than 140 kg. cal., and is thus far too small: those of the two straight chains are about the same, and are about 20 kg. cal. smaller than the observed value: the extra stability gained from the resonance may well account for the difference of 20 kg. cal.

The Alkyl and Aryl Derivatives of Hydrazoic Acid

The azidoparaffins are not at all well known; the simplest, methyl azide, has been prepared by the action of methyl sulphate on an aqueous solution of sodium azide.[4] It is evolved as a gas which can be condensed to a liquid

[1] Miss I. E. Knaggs, *Proc. Roy. Soc.* 1935, A, **150**, 576; E. W. Hughes, *J. Chem. Phys.* 1935, **3**, 1.

[2] W. A. Roth and F. Müller, *Ber.* 1929, **62**, 1190.

[3] N. V. Sidgwick, *Trans. Faraday Soc.* 1934, **30**, 801.

[4] O. Dimroth and W. Wislicenus, *Ber.* 1905, **38**, 1573.

boiling at 20°; it has a peculiar and unpleasant smell which recalls that of hydrazoic acid. Methyl azide is also formed by the action of hydrazoic acid on diazomethane,[1] a reaction like that between hydrogen chloride and diazomethane. Ethyl azide (boiling-point 48–49°) can be obtained from ethyl sulphate and is described as smelling like chloroform.[2] These compounds are quite stable at room temperature, but are apt to detonate on rapid heating. In the gas phase both methyl and ethyl azides decompose at measurable rates at temperatures between 200° and 250°; the reactions are homogeneous and unimolecular.[3] The decomposition of methyl azide appears to involve dissociation into hydrazoic acid and the methylene radical, and polymerization of the latter to ethylene.

$$CH_3 \cdot N_3 \longrightarrow N_3H + CH_2 \quad : \quad 2CH_2 \longrightarrow CH_2:CH_2$$
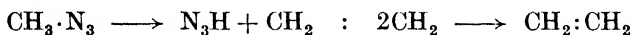
With ethyl azide the same process occurs giving hydrazoic acid and ethylene, $CH_3 \cdot CH_2 \cdot N_3 \longrightarrow CH_2:CH_2 + N_3H$, but there is also loss of nitrogen, the residue CHN rearranging in various ways. Other aliphatic azides are known, notably the α- and β-azido aliphatic esters and amides, e.g. $CH_3 \cdot CHN_3 \cdot CO_2Et$ and $CH_2N_3 \cdot CH_2 \cdot CONH_2$. They are made by the action of sodium azide on the corresponding chloro- or bromo- compounds, when the azide group replaces the halogen atom. They are colourless liquids or low-melting solids which are fairly stable, although they may explode on heating rapidly.

The aryl azides are often called in German diazoimides: thus the compound which will be described here as phenyl azide, ϕN_3, is also known as diazobenzene imide. The aryl azides can be prepared in a variety of ways, most of them starting with the aromatic diazo compounds. The first method known was that of P. Griess who discovered phenyl azide and obtained it by the action of ammonia on benzene diazonium perbromide.

$$[\phi N_2]Br_3 + NH_3 \longrightarrow \phi N_3 + 3HBr$$

The reaction is general for all the diazonium perhalides, even the tetrachloro-iodides, $[ArN_2]ICl_4$, and also for the plumbichlorides, $[ArN_2]_2PbCl_6$. The latter probably provide the most convenient route to the aryl azides.[4] The simple aryl azides are reasonably stable compounds, unless they are in contact with acids, and can be obtained from the reaction mixture by distilling in steam. Other methods of converting a diazo compound into an azide are: (i) To treat it with hydrazoic acid; this is done by adding sodium azide to the acid solution containing the diazonium salt, when the aryl azide immediately separates; the reaction resembles that whereby iodobenzene can be obtained by the immediate decomposition of the diazonium iodide (see p. 406). (ii) To treat the diazonium sulphate with

[1] E. Oliveri-Mandalà, *Gazz.* 1932, **62**, 716.

[2] H. Staudinger and E. Hauser, *Helv. Chim. Acta*, 1921, **4**, 872.

[3] H. C. Ramsperger, *J. Amer. C. S.* 1929, **51**, 2142; J. A. Leermakers, ibid. 1933, **55**, 2719.

[4] F. D. Chattaway, F. L. Garton, and G. D. Parkes, *J.C.S.* 1924, **125**, 1986.

phenylhydrazine or hydroxylamine; in either case coupling on to a nitrogen atom takes place and the product breaks down to the azide.

$$ArN_2X + \phi NH \cdot NH_2 \longrightarrow ArN\!:\!N \cdot N\phi \cdot NH_2 \longrightarrow ArN_3 + \phi NH_2$$

$$ArN_2X + NH_2OH \longrightarrow ArN\!:\!N \cdot NHOH \longrightarrow ArN_3 + H_2O$$
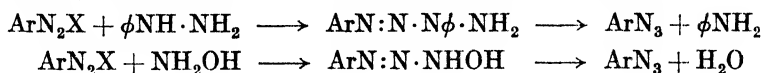
With diazonium salts which contain negative substituents, such as —NO$_2$, coupling with the potassium salt of the mono- or disulphonic acid of hydroxylamine gives the best yields, though this method is useless for aniline itself.[1] (iii) To couple the diazonium compound with a sulphonamide in the presence of caustic soda; the product is decomposed rather remarkably to a sulphinic acid and an azide.[2]

$$ArN_2X + H_2N \cdot SO_2 \cdot Ar' \longrightarrow ArN\!:\!N \cdot NH \cdot SO_2 \cdot Ar' \longrightarrow ArN_3 + Ar' \cdot SO_2H$$
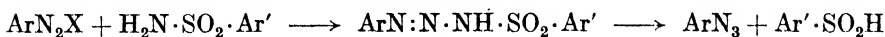
(iv) To treat the diazonium salt with a solution containing chloramine, NH$_2$Cl;[3] the reaction probably proceeds thus:

$$Ar \cdot N_2X + NH_2Cl \longrightarrow Ar \cdot N\!:\!N \cdot NHCl \longrightarrow \phi N_3 + HCl.$$
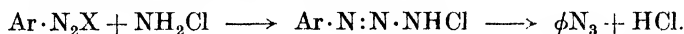
The yield is small, but if the sodium derivative of N-chlor-p-toluenesulphonamide, CH$_3 \cdot$C$_6$H$_4 \cdot$SO$_2$NClNa, replaces chloramine, very good yields can be obtained.[4]

The aryl azides can also be obtained from the monoaryl hydrazines. Gentle oxidation of these, as by mercuric oxide or hydrogen peroxide, probably converts them into *symm*-tetrazenes, ArNH$\cdot$N$:$N$\cdot$NHAr, which immediately decompose into the azide and an amine, ArN$_3$ and H$_2$NAr (compare the oxidation of the secondary hydrazines, p. 465). With nitrous acid phenylhydrazine and its analogues give nitroso compounds,

$$Ar \cdot N(NO) \cdot NH_2,$$

which are only stable at a low temperature. If treated with acids or alkalis they lose water to give azides. This reaction was discovered by E. Fischer[5] and led him to propose the cyclic formula for the azides.

$$\phi \cdot N \!\! \diagdown\!\!\!\!\!\!\!{\overset{\textstyle NO}{\underset{\textstyle NH_2}{}}} \longrightarrow \phi \cdot N \!\! \diagdown\!\!\!\!\!\!\!{\overset{\textstyle N}{\underset{\textstyle N}{\|}}}$$
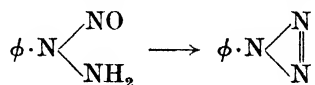
That formula being ruled out, the reaction must involve some rearrangement; similar rearrangements are not, however, unknown, since the one nitroso derivative of benzylmethylhydrazine, ϕCH$_2 \cdot$N(NO)$\cdot$NHMe, rearranges into the other, ϕCH$_2 \cdot$NH$\cdot$NMeNO, in the presence of a little acid,[6] and further the decomposition of nitrosophenyl hydrazine into nitrous oxide and aniline, which takes place on heating it in an inert solvent, suggests that the nitroso group migrates to the other nitrogen atom (see p. 379):[7]

$$\phi \cdot N(NO) \cdot NH_2 \longrightarrow \phi \cdot NH \cdot N\!:\!NOH \longrightarrow \phi NH_2 + N_2O.$$
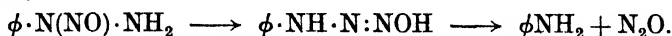
[1] H. Rupe and K. v. Majewski, *Ber.* 1900, **33**, 3408.

[2] P. K. Dutt, *J.C.S.* 1923, **123**, 269; A. Key and P. K. Dutt, ibid. 1928, 2035.

[3] M. O. Forster, ibid. 1915, **107**, 260.   [4] D.R.-P. 456857; *Zent.* 1928, ii, 3111.

[5] *Annalen*, 1877, **190**, 92.   [6] A. Angeli, *Atti R.* 1927, [vi], **5**, 732.

[7] Wieland, *Die Hydrazine*, Stuttgart, 1913, p. 23.

The aryl azides are pale yellow oils or low-melting solids insoluble in water and with a peculiar and unpleasant smell. Phenyl azide explodes if the attempt is made to distil it under ordinary pressure, but it has been distilled unchanged under reduced pressure (boiling-point 56°/16 mm.), and it can be distilled in steam.

In their reactions with alkalis the alkyl and aryl azides illustrate the resemblance between the azide group and a halogen. In most aliphatic compounds the azide group is hydrolysed off as hydrazoic acid; with some compounds hydrazoic acid is removed leaving a double bond, as in the action of alcoholic potash on β-azido-propionic ester which gives acrylic acid:

$$N_3 \cdot CH_2 \cdot CH_2 \cdot CO_2Et \longrightarrow N_3H + CH_2 : CH \cdot CO_2Et.$$
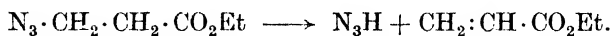
With the majority of aryl azides, the azide group cannot be removed by hydrolysis in this way, just as chlorobenzene is attacked by alkalis only with great difficulty. A compound such as 2,4-dinitrophenyl azide, however, is hydrolysed by alkalis to hydrazoic acid and dinitro-phenol, just as the introduction of nitro groups into the ortho or para position to a chlorine atom attached to a benzene ring makes that atom reactive.

The chemical reactions of the azides have been mainly studied in the aromatic series where the azide group is stable to hydrolysis. They can be divided into three main classes—decompositions, reduction and addition reactions.

A large number of the decompositions of the azides[1] proceed as though the first stage were the loss of a molecule of nitrogen and the formation of a radical containing univalent nitrogen:

$$\phi N_3 \longrightarrow \phi N \langle + N_2.$$
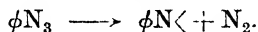
This is true for the spontaneous decomposition as well as those in the presence of acids and alkalis. Whether this is the true mechanism is unknown; the radical, if it exists, is certainly of very short life, and the reactions in which the hypothetical radical takes part are not in all respects identical with those that occur in the action of certain oxidizing agents on aniline where a similar radical is suspected (see p. 54). Nevertheless, the decompositions are best regarded as the various modes of reaction and rearrangement of the radical. A solution of phenyl azide in benzene undergoes little change on continued boiling, but if it is heated in a sealed tube, nitrogen is lost and aniline and azobenzene are formed; the latter can clearly come from the polymerization of two radicals,

$$2 \phi N \longrightarrow \phi \cdot N : N \cdot \phi,$$
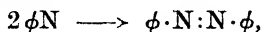
and the hydrogen needed for the formation of the aniline must come from the benzene and any traces of water present in the tube; a certain amount of brown tar is also formed at the same time. In solution in p-xylene the same products are formed, but in addition di-p-tolylethane,

$$Me \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot C_6H_4 \cdot Me,$$

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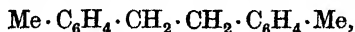
[1] A summarizing paper on this subject by A. Bertho will be found in *J. pr. Chem.* 1929, **120**, 119.

is found; this is the dehydrogenation product of two molecules of p-xylene, and its formation throws light on the source of the hydrogen needed for the production of aniline.[1] If phenyl azide is heated with sodium ethoxide in ethyl alcohol under ordinary pressure, the reaction takes another course; nitrogen is lost and the resulting radical abstracts hydrogen from the sodium ethoxide to give the sodium derivative of vinyl alcohol which condenses with unchanged azide to form phenyl-1,2,3-triazole; almost quantitative yields of the products are obtained and the method can be used for the preparation of the triazole.[2]

$$2\,\phi N_3 + CH_3 \cdot CH_2ONa \longrightarrow \phi \cdot NH_2 + N_2 + NaOH + \begin{matrix} \phi \cdot N\!-\!N \\ | \quad \| \\ HC \quad N \\ \diagdown \diagup \\ CH \end{matrix}$$
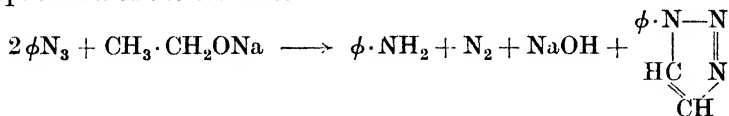
With aliphatic azides there are other possibilities of rearrangement; benzyl azide if heated with water gives the radical $\phi \cdot CH_2 \cdot N\!\!<$. This rearranges partly to benzylidene-imine which is hydrolysed to benzaldehyde and ammonia, and partly to methylene aniline which is hydrolysed to aniline and formaldehyde.[3]

$$\phi CH_2 \cdot N_3 \longrightarrow N_2 + \phi CH_2N \begin{cases} \nearrow \ \phi CH\!:\!NH \longrightarrow \phi CHO + NH_3 \\ \searrow \ \phi N\!:\!CH_2 \longrightarrow \phi NH_2 + CH_2O \end{cases}$$
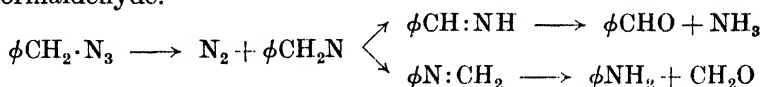
In addition to these reactions a certain amount of benzylamine,

$$\phi \cdot CH_2 \cdot NH_2,$$

is formed, most probably by the reduction of the radical by the formaldehyde. A similar decomposition takes place with other aliphatic azides.[4]

All azides decompose on heating with acids. The products obtained from the aryl azides depend on the acid and the solvent; a large variety of substances can be formed and they have been investigated in detail by E. Bamberger and his pupils.[5] The subject is too complicated for a complete discussion to be given here. Many of the products obtained resemble those formed in the acid decomposition of N-phenylhydroxylamine (see p. 163), and it was thought at one time that the first stage of the azide decomposition was $\phi N_3 + H_2O \longrightarrow \phi NHOH + N_2$ and that the decomposition products were really those of the hydroxylamine. As has been stated above, this view cannot be accepted because no azoxy compound, the typical product of the decomposition of a hydroxylamine, is ever found among the products from an azide. The similarity between the two decompositions is much more likely to arise from the fact that both series of compounds can give the same radical as a first step.

$$\phi N_3 \longrightarrow N_2 + \phi N \qquad \phi NHOH \longrightarrow H_2O + \phi N$$
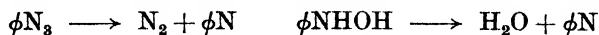
Phenyl azide is not attacked by cold hydrochloric acid, but on boiling

[1] A. Bertho, *Ber.* 1924, **57**, 1138.　　　　[2] A. Bertho, ibid. 1925, **58**, 859.

[3] T. Curtius and A. Darapsky, *J. pr. Chem.* 1901, **63**, 428.

[4] T. Curtius, *Ber.* 1912, **45**, 1058.

[5] Summarizing papers; E. Bamberger, *Annalen*, 1921, **424**, 233; 1925, **443**, 192.

nitrogen is lost and the main products are o- and p-chloroaniline; if methyl alcohol is present p-methoxyaniline is also formed.

In passing, it is of interest to mention the decomposition of hydrazoic acid itself brought about by concentrated sulphuric acid in the presence of various organic compounds.[1] Here again nitrogen is lost and the imine radical NH appears to be formed: it seems to be much more reactive than the radicals formed from the azides. In the presence of benzene, aniline is formed together with hydroxylamine and hydrazine;

$$\phi H + NH \longrightarrow \phi NH_2$$

$$NH + H_2O \longrightarrow NH_2OH$$

$$2NH \longrightarrow NH:NH; \quad 2NH:NH \longrightarrow N_2 + NH_2 \cdot NH_2.$$
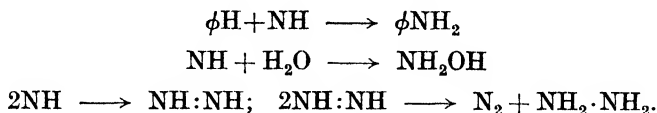
Ketones are converted into amides, and with cyclic ketones the same reaction takes place, the ring being enlarged.

$$R \cdot CO \cdot R + NH \longrightarrow R \cdot CO \cdot NHR$$
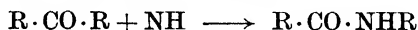
The reaction with β-ketonic esters such as acetoacetic ester can be used for the synthesis of amino-acids.

$$Me \cdot CO \cdot CHR \cdot CO_2Et + NH \longrightarrow Me \cdot CO \cdot NH \cdot CHR \cdot CO_2Et$$

$$\xrightarrow{H_2O} Me \cdot CO_2H + H_2N \cdot CHR \cdot CO_2H$$

Some of these very remarkable reactions are similar to those of diazomethane where the radical CH_2 is presumably the reagent (see p. 354). The most important application of this reaction is to the conversion of a carboxyl group into an amino group. If a carboxylic acid is dissolved in concentrated sulphuric acid and shaken with a benzene or chloroform solution of hydrazoic acid, nitrogen and carbon dioxide are evolved and the amine formed; it can be liberated from the acid solution after it has been poured on ice.[2]

$$R \cdot CO_2H + HN_3 \longrightarrow RNH_2 + N_2 + CO_2$$
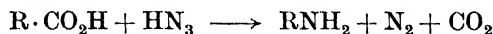
The method can be used in both the aromatic and aliphatic series and often gives as much as 80 per cent. of the theoretical yield. Dibasic acids give diamines; thus adipic acid is converted into putrescine (1,4-diaminobutane).

The reduction of the aliphatic and aromatic azides gives different products according to the reagent and conditions which are used. With zinc and sulphuric acid phenyl azide is reduced to aniline and ammonia, but with the majority of other reagents the products are aniline and nitrogen. This reaction is most conveniently carried out either by using hydrogen in the presence of colloidal palladium[3] or amalgamated aluminium in aqueous ammonia,[4] and is general for azides of all types. It can be used for showing the presence of the azide group; thus cyanuric azide (II) might

[1] K. F. Schmidt, *Ber.* 1924, **57**, 704.

[2] J. von Braun, *Annalen*, 1931, **490**, 125; M. Oesterlin, *Z. angew. Chem.* 1932, **45**, 536.   [3] H. Wienhaus and H. Ziehl, *Ber.* 1932, **65**, 1461.

[4] K. Freudenberg, H. Eichel, and F. Leutert, ibid. p. 1188.

be a tri-tetrazole (I), but this structure is excluded, since it is smoothly reduced with hydrogen and palladium to melamine (III).

I.   II.   III.
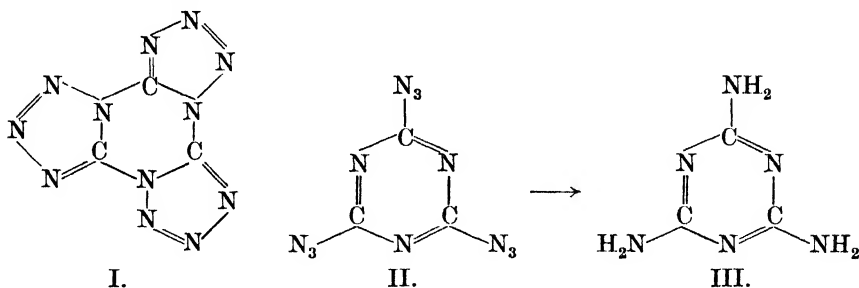
The reaction is also useful for the synthesis of peptides (p. 126). α-Azido-propionyl chloride, $CH_3 \cdot CHN_3 \cdot COCl$, and azidoacetyl chloride,

$$CH_2N_3 \cdot COCl,$$
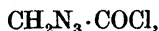
can both be obtained and condensed with an amino-acid: the resulting azidoacetyl (or propionyl) compound can then be reduced to an amino-acid and the process repeated:

$$N_3 \cdot CH_2 \cdot COCl + NH_2 \cdot CH_2 \cdot CO_2H \longrightarrow N_3 \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H$$
$$\longrightarrow H_2N \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H.$$
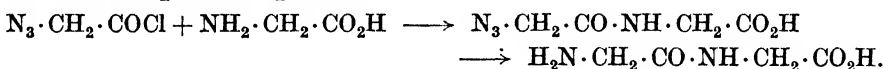
These reductions involve the disintegration of the azido group. Dimroth, however, found[1] that if phenyl azide is reduced with an ethereal solution of stannous chloride at —20°, phenyl triazene, $\phi \cdot N:N \cdot NH_2$ can be obtained. It is an extremely unstable compound which on warming or in contact with almost every reagent breaks up into aniline and nitrogen: $\phi \cdot N:N \cdot NH_2 \longrightarrow \phi NH_2 + N_2$.

The addition reactions of the azides, which have been mainly studied with phenyl azide, can be divided into two classes, those in which addition takes place to a compound containing a reactive methylene or methine group, that is compounds which are capable of tautomerism of the keto-enol type, and those in which it takes place to an ethylene or an acetylene.

The first class of addition reactions leads to a derivative of 1-phenyl-1,2,3-triazole. Hydroxy, amino, or ketonic derivatives are formed according to the constitution of the starting material.[2] All these condensations take place in alcohol in the presence of sodium ethoxide and in the majority of cases the sodium derivative of the methylene compound is undoubtedly the substance that reacts. The condensations are similar to those of aliphatic diazo compounds which lead to pyrazole derivatives. As illustrations the condensations with acetoacetic ester, malonic ester, dibenzoylmethane, and cyanacetic ester will be quoted.

1-phenyl-5-methyl-1,2,3-triazole-4-carboxylic ester
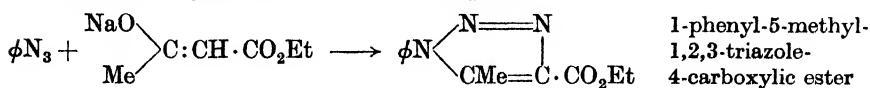
[1] Ibid. 1907, **40**, 2376.

[2] O. Dimroth, ibid. 1902, **35**, 1029, 4041; 1903, **36**, 909; 1905, **38**, 670.

$$\phi N_3 + \underset{NaO}{\overset{EtO}{>}} C:CH \cdot CO_2Et \longrightarrow \phi N \underset{\underset{OH}{|}}{\overset{N=N}{\diagdown}} \underset{C=C \cdot CO_2Et}{|}$$

1-phenyl-5-hydroxy-
1,2,3-triazole-
4-carboxylic ester

$$\phi N_3 + \underset{\phi}{\overset{NaO}{>}} C:CH \cdot CO\phi \longrightarrow \phi N \underset{C\phi=C \cdot CO \cdot \phi}{\overset{N=N}{\diagdown}}$$

1,5-diphenyl-
4-benzoyl-
1,2,3-triazole

$$\phi N_3 + CN \cdot CH_2 \cdot CO_2Et \longrightarrow \phi N \underset{\underset{NH_2}{|}}{\overset{N=N}{\diagdown}} \underset{C=C \cdot CO_2Et}{|}$$

1-phenyl-5-amino-
1,2,3-triazole-
4-carboxylic ester
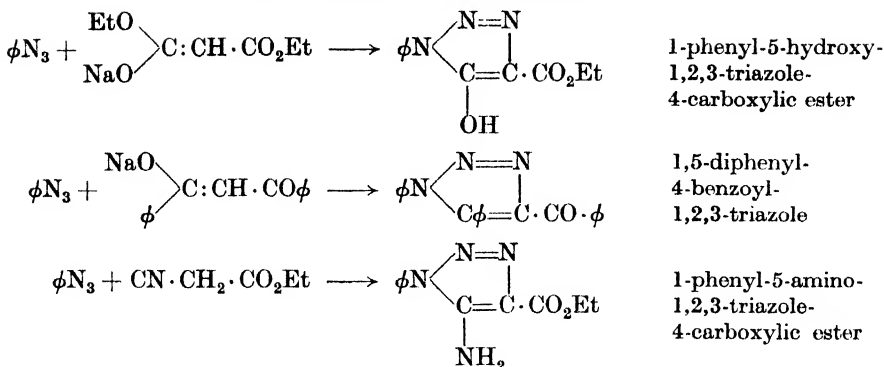
The 5-hydroxy and 5-amino triazoles are particularly interesting because they are tautomeric compounds, the tautomeric change involving the opening of the triazole ring and the formation of an aliphatic diazo group (see p. 351). It is remarkable that a condensation reaction of the same type takes place with acetic and propionic esters leading to a 5-hydroxytriazole.

$$\phi N_3 + EtO_2C \cdot CH_2R \longrightarrow \phi N \underset{\underset{OH}{|}}{\overset{N=N}{\diagdown}} \underset{C=CR}{|}$$
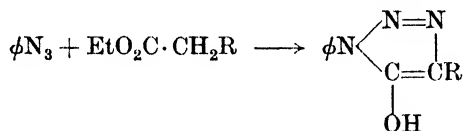
The mechanism of these condensations is somewhat obscure, but the first stage may be the formation of a diazoamino compound,

$$\phi N_3 + CH_2 \underset{R'}{\overset{R}{<}} \longrightarrow \phi NH \cdot N:N \cdot CH \underset{R'}{\overset{R}{<}}$$
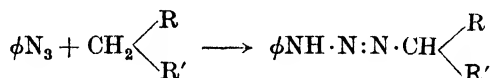
which is followed by ring closure. There is no reaction at temperatures up to 100° in the absence of sodium ethoxide. At 170°, however, benzyl azide reacts with malonic ester[1] to form nitrogen and benzylamino-malonic ester; this is probably a reaction of the free radical:

$$\phi CH_2 \cdot N{<} + CH_2(CO_2Et)_2 \longrightarrow \phi \cdot CH_2 \cdot NH \cdot CH(CO_2Et)_2.$$
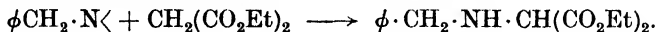
The addition of phenyl azide to unsaturated compounds leads to triazoles or triazolines but takes place much less readily than the very similar addition of aliphatic diazo compounds, which gives pyrazole and pyrazoline compounds. Thus while diazo methane and acetylene combine rapidly at 0° (see p. 357), the formation of phenyl triazole from phenyl azide and acetylene only takes place if the components are heated in acetone solution in a sealed tube at 100° for 70 hours.[2]

$$\phi N_3 + CH:CH \longrightarrow \underset{\underset{CH-N}{\|\qquad\|}}{\overset{\phi N}{\diagup \diagdown}} \underset{CH \qquad N}{}$$
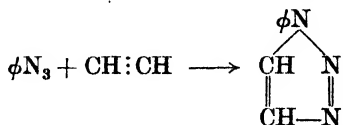
[1] T. Curtius and G. Ehrhart, *Ber.* 1922, **55**, 1559.

[2] O. Dimroth and G. Fester, ibid. 1910, **43**, 2219.

Again diazoacetic ester will combine with benzene (p. 357), but no case is known of an azide reacting with an aromatic system. The conditions which determine whether addition takes place or not are not fully known, but in general it can be said that if a double bond is conjugated with an aromatic nucleus the addition takes place much less readily, while if the double bond is in a cyclic system in which there is any considerable ring-strain, the addition product is formed very easily. Phenyl azide will condense with fumaric ester and with styrene at higher temperatures to give 1-phenyl-triazoline-4,5-dicarboxylic ester and diphenyltriazoline, respectively,[1] but does not react with stilbene, $\phi \cdot CH : CH \cdot \phi$, or cinnamic ester, $\phi \cdot CH : CH \cdot CO_2Et$.

$$
\begin{array}{c}
EtO_2C \cdot CH \\
\parallel \\
HC \cdot CO_2Et
\end{array}
+ \phi N_3 \longrightarrow
\begin{array}{c}
N\phi \\
\diagup \quad \diagdown \\
N \qquad CH \cdot CO_2Et \\
\parallel \qquad \mid \\
N \text{---} CH \cdot CO_2Et
\end{array}
$$

$$
\begin{array}{c}
\phi \cdot CH \\
\parallel \\
CH_2
\end{array}
+ \phi N_3 \longrightarrow
\begin{array}{c}
\phi N \\
\diagup \quad \diagdown \\
N \qquad CH\phi \\
\parallel \qquad \mid \\
N \text{---} CH_2
\end{array}
$$
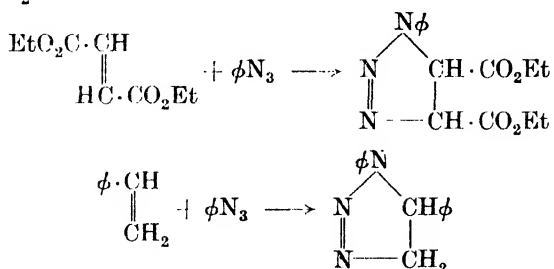
The cyclic unsaturated hydrocarbons in which the reaction takes place extremely readily are bicyclic substances of the type (IV).[2]

$$
\begin{array}{c}
\text{CH} \\
CH \quad \mid \quad CH_2 \\
\parallel \quad CH_2 \quad \mid \\
CH \quad \mid \quad CH_2 \\
\text{CH}
\end{array}
\longrightarrow
\begin{array}{c}
\text{CH} \\
\phi N \text{---} CH \quad \mid \quad CH_2 \\
N \diagdown \quad \mid \quad CH_2 \quad \mid \\
\quad CH \quad CH_2 \\
\text{CH}
\end{array}
$$

IV.   V.
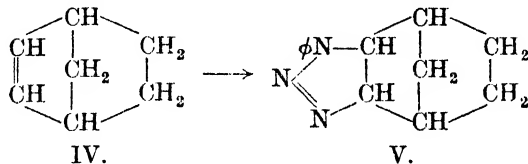
If a compound containing the elements of this structure is mixed with phenyl azide in the cold, the addition product (V) crystallizes out in a few minutes, and the reaction can be used to test for the presence of such a structure. A monocyclic compound such as cyclohexene does not react so readily, but even in this series the rate of addition is greatest with cyclopentene (VI) and less with the higher members containing six, seven, or eight atoms in the ring, when the ring-strain is smaller.

$$
\begin{array}{c}
CH_2 \\
CH \quad \diagdown \\
\parallel \qquad CH_2 \\
CH \quad \diagup \\
CH_2
\end{array}
\qquad
\begin{array}{c}
CH \\
CH \quad \mid \quad CH_2 \\
\parallel \quad CH_2 \quad \mid \\
CH \quad \mid \quad CH_2 \\
CH
\end{array}
\qquad
\begin{array}{c}
CH \\
CH \quad \mid \quad CH_2 \\
\parallel \quad CMe_2 \quad \mid \\
CH \quad \mid \quad CH_2 \\
CH
\end{array}
$$

VI.   VII   VIII.
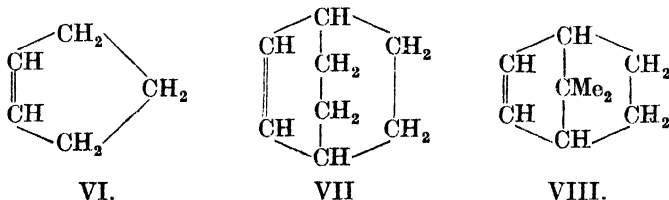
At the same time it must be mentioned that certain observations of Alder

[1] L. Wolff, *Annalen*, 1912, **394**, 69.

[2] K. Alder and G. Stein, ibid. 1931, **485**, 211; 1933, **501**, 1.

and Stein are more difficult to interpret. If in the bicyclic hydrocarbons the bridge consists of two methylene groups as in bicyclo-octene (VII), the rate of addition is very small: the ring-strain in this system is certainly less than in the bicyclo-heptene (IV). On the other hand, if the hydrogen atoms of the bridge are replaced by methyl groups as in (VIII), the ease of addition at once disappears. Just as the pyrazolines obtained by the addition of aliphatic diazo compounds and ethylenes lose nitrogen (see p. 357), so the triazolines lose nitrogen on heating and give rise to substances which are mentioned later (see p. 471). As well as these bicyclic hydrocarbons, quinones will add on one or two molecules of an aryl azide.[1] Toluquinone and phenyl azide slowly react at 50° to give the triazoline (IX) which, if heated above 100°, loses nitrogen and forms the ethylene imine (X).[2]

IX.   X.
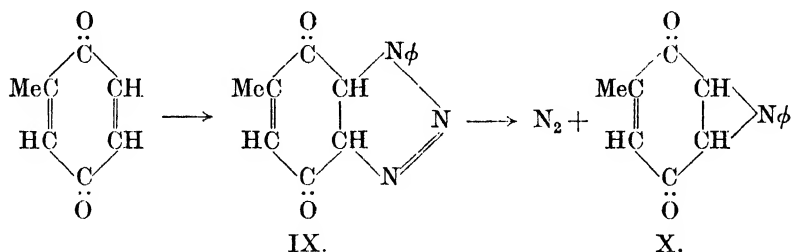
Finally two addition reactions of a different type will be mentioned. If an alkyl or aryl azide is treated with a tertiary phosphine in an inert solvent, a complex which contains one molecule of each is formed and can be isolated in certain cases;[3] in most cases it loses nitrogen at once and gives a phosphinimine which is basic and readily hydrolysed to a phosphine oxide and an amine. The reactions must be formulated thus:

$$R_3P + R'N_3 \longrightarrow R_3P{\to}N \cdot N{:}N \cdot R' \longrightarrow N_2 + R_3P{\to}NR'$$
$$\longrightarrow R_3P{\to}O + H_2NR'.$$
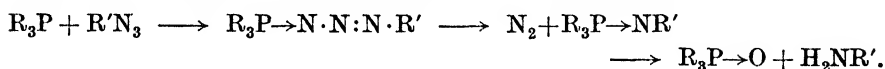
The constitution of the phosphinimine is rather like that of a sulphilimine (p. 160). Azides react with Grignard compounds to give diazoamino compounds, a reaction which is mentioned below (p. 458).

The Acyl Derivatives of Hydrazoic Acid

These compounds can be regarded as derivatives of acids in which the acidic hydroxyl group has been replaced by an azide group. Thus we have acetazide, $CH_3 \cdot CO \cdot N_3$, and benzene sulphonazide, $\phi \cdot SO_2 \cdot N_3$. Our knowledge of the group is largely due to the work of Curtius and his pupils.[4] There are two general methods of preparation. The first, the action of

[1] L. Wolff, *Annalen*, 1912, **394**, 70; 1913, **399**, 274.
[2] F. D. Chattaway and G. D. Parkes, *J.C.S.* 1925, **127**, 1307.
[3] H. Staudinger and E. Hauser, *Helv. Chim. Acta*, 1921, **4**, 862.
[4] See the obituary notice of Curtius by A. Darapsky, *J. pr. Chem.* 1930, **125**, 1.

nitrous acid or nitrous fumes on the hydrazide of the acid, was discovered
by Curtius.

$$\phi \cdot CO \cdot NH \cdot NH_2 + ONOH \longrightarrow \phi \cdot CO \cdot N_3 + 2H_2O$$

It has been largely replaced by the second method which is more con-
venient when sodium azide can be obtained; it consists simply in the
interaction of sodium azide and an acid chloride; aqueous acetone is often
a good solvent for the reaction.[1]

$$\phi \cdot CO \cdot Cl + NaN_3 \longrightarrow \phi \cdot CON_3 + NaCl$$
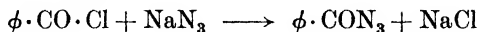
The azides of the lower fatty acids are unstable volatile liquids, while those
of the simpler aromatic acids are solids which melt at distinctly lower
temperatures than the corresponding amides.[2] They are usually sparingly
soluble in water but easily soluble in organic solvents. All the acyl azides
are somewhat explosive in the solid state, but in varying degrees: benz-
azide explodes only on rapid heating, but the diazide of carbonic acid,
$CO_2(N_3)_2$, detonates when it is gently rubbed with a glass rod.[3] The acid
azides are hydrolysed by alkalis and acids to hydrazoic acid and the acids
from which they are derived, although a certain amount of the compound
usually undergoes the Curtius rearrangement, which is the most interesting
reaction of these azides.

The acyl azides can be divided into two classes, those which show the
Curtius rearrangement to an isocyanate with loss of nitrogen, and those
which do not. The latter class have been called by Curtius 'starre' azides,
that is rigid azides, although they include many of the most explosive
compounds and are not stable in the ordinary sense. They are rigid in the
sense that the radical formed in their decomposition by loss of nitrogen
does not immediately rearrange but shows reactions which are somewhat
similar to those of the radical $\phi \cdot N\langle$ which seems to be formed in the
decomposition of phenyl azide: hydrogen, for example, can be taken from
an aromatic hydrocarbon.[4] This class includes all the sulphonazides,
$R \cdot SO_2N_3$, the diazides of carbonic acid, $CO(N_3)_2$, and of sulphuric acid,
$SO_2(N_3)_2$, and the azides of carbamic acid and phenyl carbamic acid,
$H_2N \cdot CO \cdot N_3$ and $HN\phi \cdot CO \cdot N_3$.

All other known azides, that is the azides of all the carboxylic acids
except those mentioned, undergo the Curtius rearrangement when they
decompose on heating in a solvent. This is essentially a rearrangement
to an isocyanate of the radical formed by the loss of nitrogen:

$$R \cdot CO \cdot N_3 \longrightarrow N_2 + R \cdot CO \cdot N \longrightarrow RN:CO.$$
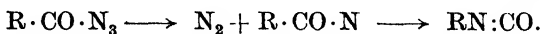
In many cases the isocyanate can be isolated, as when benzazide is heated
on the water-bath in benzene solution. With other solvents the product
of a further reaction of the isocyanate is obtained; thus in alcohol a urethane

[1] G. Powell, *J. Amer. C. S.* 1929, **51**, 2436.

[2] e.g. $\phi CO \cdot N_3$, melting-point 32°; $\phi CO \cdot NH_2$, melting-point, 130°.

[3] T. Curtius and A. Bertho, *Ber.* 1926, **59**, 565.

[4] T. Curtius and F. Schmidt, ibid. 1922, **55**, 1571.

is normally formed, while in water the isocyanate may be hydrolysed to carbon dioxide and an amine.

$$RN:CO + EtOH \longrightarrow RNH \cdot CO_2Et$$
$$RN:CO + H_2O \longrightarrow RNH_2 + CO_2$$
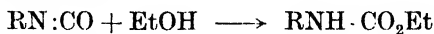
In the latter case the amine usually reacts to some extent with the isocyanate to give a substituted urea.

$$RN:CO + RNH_2 \longrightarrow RNH \cdot CO \cdot NHR$$
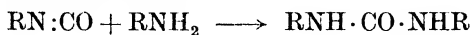
All these products are hydrolysed to the amine, RNH_2, by boiling with a mineral acid, so that the Curtius rearrangement serves as a method for effecting the change $R \cdot CO_2H \rightarrow R \cdot NH_2$, just as the Hofmann rearrangement does (p. 17). It can also be used in order to make certain that an acidic hydroxyl group forms part of a carboxyl group.[1]

For preparative purposes the reaction can be carried out without isolating the azide,[2] and gives good yields with acids of all kinds. The acid chloride is stirred with dry sodium azide in benzene and warmed: nitrogen is evolved and the isocyanate is formed. Aqueous hydrochloric acid is added and the whole boiled: after distilling off the benzene the hydrochloride of the amine is obtained from its aqueous solution. With the lower amines it is better to use glacial acetic acid instead of hydrochloric acid, because it is easier to isolate the acetyl amine which is formed by the reaction:

$$RN:CO + Me \cdot CO_2H \longrightarrow CO_2 + RNH \cdot COMe.$$
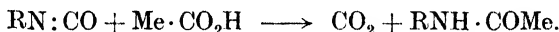
The ease with which the Curtius rearrangement takes place varies widely; some azides must be boiled in a solvent for many hours before the change is complete, while with others it is so rapid at room temperature that the azide can hardly be isolated. With the diazide of phthalic acid (I), the change takes place in the solid state; the substance can be obtained crystalline by adding ligroin to its ice-cold benzene solution, but when the
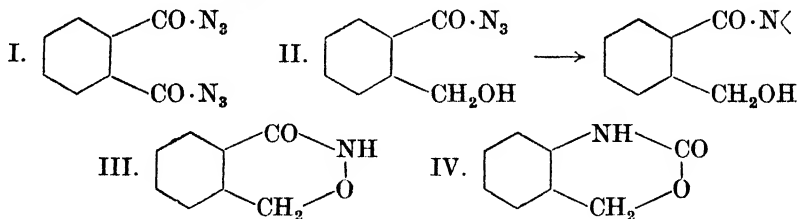
crystals become dry and reach room temperature they begin to jump about as they evolve nitrogen and, if there is more than 0·5 gram of the compound, the decomposition becomes so rapid that the crystals detonate violently.[3] The product of the decomposition is a mono-isocyanate and only one azide group has decomposed; the other is much more stable and

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[1] For the application of the test to an important degradation product of strychnine see K. N. Menon and R. Robinson, *J.C.S.* 1931, 773.

[2] C. Naegeli, L. Grüntuch, and P. Lendorff, *Helv. Chim. Acta*, 1929, **12**, 227.

[3] H. Lindemann and W. Schulteis, *Annalen*, 1928, **464**, 237.

decomposes only slowly in boiling benzene. The mechanism of the change has been the subject of much discussion. There is general agreement that in essence it is the loss of nitrogen followed by a rearrangement of the radical that remains, and the point which is obscure is how this rearrangement takes place. The radical appears to have an extremely short life and shows no chemical reactions beyond its rearrangement. Such reactions have been ingeniously looked for by taking the azides of aromatic acids in which there is a group in the ortho position with which reaction might take place before rearrangement.[1] Thus hydroxymethyl-2-benzoyl azide (II) might give the 1,2-oxazine derivative (III) but in fact the 1,3-oxazine derivative (IV) alone is formed, and a similar result has been found in other cases. There is no evidence that in the rearrangement of the radical $R \cdot CO \cdot N\langle$ the radical R becomes detached and exists as such for any finite time. This radical would be a carbon radical presumably of the type of triphenylmethyl, unless, as has been suggested,[2] it is split off as a positive ion, and for this there is no evidence. As a carbon radical it might form an addition compound with triphenylmethyl, but the course of the rearrangement of an acid azide is completely unaffected by the addition of triphenylmethyl to the solution.[3] The only conclusion that can be drawn from the experimental facts is that very probably the radical $R \cdot CO \cdot N\langle$ rearranges immediately it is formed by a purely intramolecular mechanism of which the details are not known.

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[1] Lindemann and Schulteis, loc. cit.

[2] L. W. Jones and E. S. Wallis, *J. Amer. C. S.* 1926, **48**, 169.

[3] G. Powell, ibid. 1929, **51**, 2436; E. S. Wallis, ibid. p. 2982.

HYDRAZINE DERIVATIVES[1]

OWING to the marked differences in their behaviour the organic derivatives of hydrazine are best divided into the following classes:

(1) Those which contain an —NH_2 group, i.e. the monoalkyl and mono-aryl hydrazines, $RNH \cdot NH_2$, and the 'unsymmetrical' di-substituted hydrazines $RR'N \cdot NH_2$. The two nitrogen atoms of hydrazine are best indicated as N and N', and hence the latter compounds will be described as N,N-di-substituted hydrazines.

(2) The symmetrical or N,N'-di-substituted hydrazines of formula $RNH \cdot NHR'$, which are often described as hydrazo compounds.

(3) The tri- and tetra-substituted compounds. These substances show startlingly different properties from those of the first two classes.

(4) The hydrazones, in which a divalent carbon radical replaces the two hydrogen atoms attached to one nitrogen atom, e.g. $\phi \cdot CH : N \cdot NHR$, and the azines, $R \cdot CH : N \cdot N : CH \cdot R$, which contain two such substituents.

(5) The acyl derivatives of hydrazine, which include the hydrazides, $R \cdot CO \cdot NH \cdot NH_2$, and the hydrazidines, $R \cdot C(:N \cdot NH_2) \cdot NH \cdot NH_2$.

(1) *The Mono- and N,N-Di-alkyl and Aryl Hydrazines*

The simple mono-alkyl hydrazines such as methyl and ethyl hydrazine resemble the parent substance fairly closely. They are colourless liquids which fume in air, dissolve in water with the evolution of heat, and are corrosive, rapidly attacking cork. They can be obtained in a variety of ways. The direct alkylation of hydrazine with an alkyl iodide gives a certain amount of methylhydrazine, but the reaction is difficult to stop at this stage and N,N-dimethyl hydrazine is the main product. It has been observed that alkylation of a hydrazine always takes place on the more basic of the two nitrogen atoms. When hydrazine itself is methylated, the methylhydrazine first formed contains a more basic nitrogen atom than the unattacked hydrazine, so that methylation to the dimethyl compound occurs more easily than monomethylation of the hydrazine. In consequence the method, though admirable for preparing dimethyl hydrazine, gives poor yields of the monomethyl compound. The probable explanation for the preferential alkylation of the more basic atom is that the reaction involves the formation of a quaternary halide:

$$NH_2 \cdot NHR + MeI \longrightarrow [NH_2 \cdot NHRMe]I \longrightarrow NH_2 \cdot NRMe + HI.$$

Methylhydrazine is best prepared by J. Thiele's method:[2] hydrazine is condensed with benzaldehyde and the azine is treated with methyl

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[1] The interesting monograph by Wieland, *Die Hydrazine*, Stuttgart, 1913, is still very useful.　　　　　　　　　　　　　　　　　[2] *Annalen*, 1910, **376**, 244.

sulphate. The resulting methosulphate breaks up when heated with water to give methylhydrazine, methyl hydrogen sulphate and benzaldehyde:

$$2\phi \cdot CHO + H_2N \cdot NH_2 \longrightarrow \phi \cdot CH:N \cdot N:CH \cdot \phi$$

$$\longrightarrow \phi \cdot CH:N \cdot NMe:CH\phi[SO_4Me] \longrightarrow NHMe \cdot NH_2 + 2\phi \cdot CHO + MeHSO_4.$$
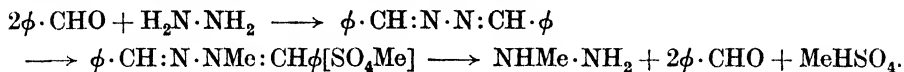
It is also formed in the reduction of diazomethane,

$$CH_2N_2 \longrightarrow CH_3 \cdot NH \cdot NH_2,$$
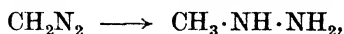
and in the preparation of diazomethane from hydrazine and chloroform owing to the interaction of some of the diazomethane with unchanged hydrazine (see p. 351).

There are two useful methods for obtaining alkylhydrazines which are of general application. The first is the method of P. Schestakov:[1] just as an amide $R \cdot CONH_2$ is converted into the amine $R \cdot NH_2$ by the Hofmann reaction with sodium hypochlorite (see p. 146), so from an N-alkyl urea, $RNH \cdot CONH_2$, the substituted hydrazine, $RNH \cdot NH_2$, can be obtained. The second method is due to N. Kijner:[2] if the bromo-amine (see p. 40) derived from an amine of formula $RCH_2 \cdot NH_2$ or $RR'CH \cdot NH_2$ is treated with silver oxide, the elements of hydrogen bromide are removed and two of the resulting radicals condense to an azo compound. This rearranges very rapidly into the isomeric hydrazone. The latter can be hydrolysed to the ketone (or aldehyde) and the hydrazine.

$$2RR'CH \cdot NHBr \xrightarrow{-2HBr} RR'CH \cdot N:N \cdot CHRR'$$

$$\longrightarrow RR'C:N \cdot NH \cdot CHRR' \longrightarrow RR'CO + H_2N \cdot NH \cdot CHRR'$$
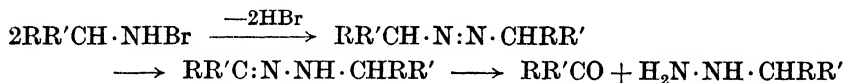
The alkyl hydrazines are strong monacidic bases and vigorous reducing agents, reducing Fehling's solution in the cold. On oxidation they give nitrogen and a hydrocarbon, probably through the intermediate formation of a derivative of diimide:

$$RNH \cdot NH_2 \longrightarrow RN:NH \longrightarrow RH + N_2.$$
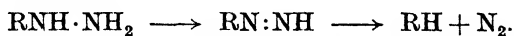
Nitrous acid attacks the secondary nitrogen atom to give an N-nitroso compound, $R \cdot N(NO) \cdot NH_2$, which is a relatively stable crystalline compound. The structure of these compounds is shown by the fact that they condense with aldehydes and other substances containing a carbonyl group to give a hydrazone, just as phenylhydrazine does. Hence one nitrogen atom must be attached to two hydrogen atoms, and the structure cannot be $RNH \cdot NH(NO)$ or any tautomeric form of this. Further action of nitrous acid, in the form of an alkyl nitrite and alkali, gives the unstable aliphatic diazotate, which, as is discussed above (p. 348), passes readily into an aliphatic diazo compound. The reaction would be expected to take place as follows, and give a compound containing four linked nitrogen atoms:

$$RN(NO) \cdot NH_2 + ONOH \longrightarrow RN(NO) \cdot N:NOH \longrightarrow RN(NO) \cdot N:NONa.$$

All compounds, however, which contain the grouping $-NR \cdot N:NOH$

[1] Z. angew. Chem. 1903, 16, 1061.　　　[2] J. pr. Chem. 1901, 64, 125.

immediately lose nitrous oxide, so that the actual product is a diazotate, $RN(NO) \cdot N:NONa \longrightarrow N_2O + RN:NONa$.

The N,N-dialkyl hydrazines, such as dimethylhydrazine, $Me_2N \cdot NH_2$, are best prepared by the reduction of the corresponding nitrosamines, $R_2N \cdot NO$; the best reagent is zinc and acetic acid, since with stronger acids the nitrosamines are decomposed to the amine (see p. 452). They resemble the monoalkyl compounds in their physical properties. They are decomposed by nitrous acid with formation of nitrous oxide,

$$R_2N \cdot NH_2 \longrightarrow R_2N \cdot N:NOH \longrightarrow R_2NH + N_2O,$$
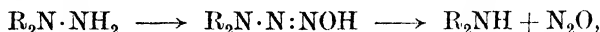
and are oxidized to symmetrical tetrazenes (see p. 465).

The best known organic derivative of hydrazine is phenylhydrazine, $\phi NH \cdot NH_2$, the simplest of the aryl hydrazines. It was discovered in 1877 by Emil Fischer,[1] and soon proved to be one of the most valuable reagents in organic chemistry. The most striking illustration of its importance is that before phenylhydrazine was known, the chemistry of the sugar group was to a large extent an unsolved and insoluble problem, but with the aid of phenylhydrazine Fischer was able to disentangle the main threads in a surprisingly short time. The preparation of phenylhydrazine was a consequence of P. Griess's discovery of the diazo compounds in 1869. It had been found that from benzene-diazonium chloride and sodium or potassium sulphite a compound could be obtained, which is now known to be the alkali diazosulphonate, $\phi \cdot N:N \cdot SO_3K$, and that this was reduced by more sulphite. In 1877 E. Fischer showed[2] that the resulting compound is the salt of phenylhydrazine sulphonic acid, $\phi NH \cdot NH \cdot SO_3Na$, and on boiling with hydrochloric acid it is hydrolysed to phenylhydrazine and sulphuric acid.

All the more important methods of preparing the monoaryl hydrazines consist in the reduction of a diazo compound, and since any primary aromatic amine can be diazotized, hydrazines containing variously substituted aryl groups can be readily obtained. The reduction can be carried out in several ways. Fischer's original method of reducing the diazosulphonate with sulphite can be used. Certain diazo compounds, such as that derived from p-nitraniline, give a hydrazine disulphonate, and not a monosulphonate, but these are hydrolysed to the hydrazine, so that the method of preparation is unaffected.[3]

$$O_2N \cdot C_6H_4 \cdot NH \cdot N(SO_3K)_2 \longrightarrow O_2N \cdot C_6H_4 \cdot NH \cdot NH_2 + 2KHSO_4$$
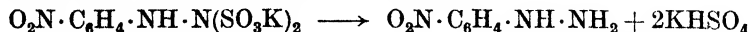
In some cases it is better to reduce the diazosulphonate with zinc dust and acetic acid or with sodium hydrosulphite.[4] Alternatively the diazonium salt can be reduced directly to the hydrazine with stannous chloride in acid solution. This method, which was discovered by Victor Meyer, is often very convenient, because the hydrazine hydrochlorides are sparingly

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[1] See K. Hoesch, 'Life of E. Fischer', *Ber.* 1921, **54**, suppl. 206; M. O. Forster, Emil Fischer Memorial Lecture, *J.C.S.* 1920, **117**, 1157.

[2] *Annalen*, **190**, 71.   [3] W. Davies, *J.C.S.* 1922, **121**, 715.

[4] L. Thompson, *J. Soc. Dyers and Colour.* 1921, **37**, 7.

soluble in hydrochloric acid and crystallize out from the reaction mixture; the method is, of course, unsuitable if easily reduced groups, such as the nitro group, are present.

Other methods are known for obtaining aryl hydrazines which do not involve the diazo compounds, and these are useful in special cases. Naphthylhydrazines can be prepared by heating the naphthols with hydrazine, but with a phenol in place of a naphthol the yield of substituted hydrazine is poor; there is a similar difference in the yield of amine obtained by the action of ammonia on the naphthols and the phenols (see p. 48). Again the chlorine atom in a compound such as chlorobenzene is too inert to react with hydrazine, but the valuable reagent 2,4-dinitrophenylhydrazine is best made by the action of 2,4-dinitrochlorobenzene on hydrazine, because the reactivity of the chlorine atom is increased by the nitro groups (see p. 258).[1]

The aryl hydrazines are liquids or low-melting solids which are colourless when pure, but like many organic bases they usually turn brown on standing in the air. They are insoluble in water and alkalis, but dissolve in dilute acids. They behave as monoacidic bases, but are much weaker than the alkyl derivatives, just as aniline is a weaker base than ammonia while methylamine is stronger. The same effect of the phenyl group is also shown by the fact that the sodium derivative ϕNNa$\cdot$NH$_2$ is obtained by the action of phenylhydrazine on sodamide.[2] The sodium derivative is also formed by the action of sodium on phenylhydrazine, but the hydrogen displaced reduces some of the phenylhydrazine to aniline: it is a pale yellow compound which is not stable in air and, somewhat surprisingly, can be recrystallized from benzene. It reacts with alkyl halides to give the N-alkyl-N-phenylhydrazine, ϕNAlk$\cdot$NH$_2$. Phenylhydrazine decomposes slowly at its boiling-point (242°) into aniline, ammonia, nitrogen, and benzene,[3]

$$2\,\phi\text{NH}\cdot\text{NH}_2 \longrightarrow \phi\text{NH}_2 + \phi\text{H} + \text{N}_2 + \text{NH}_3.$$

Since its melting-point (20°) is too low to permit easy recrystallization, it is best purified by distillation under reduced pressure. The same decomposition takes place at a much lower temperature in the presence of cuprous chloride, with which it forms an unstable complex.[4] Phenylhydrazine is a somewhat poisonous substance and long-continued exposure to its vapours is dangerous. Emil Fischer found this to his cost, and after many years' work with the compound suffered from the chronic eczema which it caused. At one time he was so sensitive to it that it had to be banned entirely from his laboratory.

The action of alkyl halides on phenylhydrazine differs from their action on the monoalkyl hydrazines. In the latter case the substituted nitrogen atom is the more basic, so that further substitution takes place on that

[1] *Organic Syntheses*, 1933, **13**, 36.
[2] A. W. Titherley, *J.C.S.* 1897, **71**, 461.
[3] F. D. Chattaway and M. Aldridge, *J.C.S.* 1911, **99**, 404.
[4] A. E. Arbusov and W. M. Tichvinsky, *Ber.* 1910, **43**, 2295.

atom, with the formation of an N,N-dialkyl-hydrazine. With phenyl-hydrazine, however, the N-phenyl-N'-alkyl-hydrazine, ϕNH·NHAlk, is the main product. The reason for this is that the phenyl group reduces the basicity of the nitrogen atom to which it is attached, so that the primary amino group is the more basic of the two and alkylation takes place there. The difference in the behaviour of the alkyl and aryl hydrazines is related to the facts that the alkylamines are stronger bases than ammonia and the arylamines weaker.

Phenylhydrazine is stable to reducing agents such as stannous chloride, but is reduced to aniline and ammonia by reagents of the type which can liberate hydrogen, such as zinc and sulphuric acid. It will act as an oxidizing agent towards certain organic groups that can be dehydrogenated, notably in the formation of an osazone of a sugar (see below); on the other hand it is extremely readily oxidized and is sometimes used as a reducing agent. The product obtained when it is oxidized depends on the reagent and the conditions. In neutral solution with copper sulphate (which is reduced to metallic copper) or ferric chloride,[1] benzene and nitrogen are formed, probably via the diimide:

$$\phi \cdot NH \cdot NH_2 \longrightarrow \phi \cdot N{:}NH \longrightarrow \phi \cdot H + N_2.$$
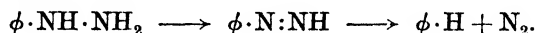
In acid solution the product is a diazonium salt which can be obtained at a low temperature, but which often decomposes during the oxidation. Chlorine and bromine react with phenylhydrazine at low temperatures as oxidizing agents, giving benzene diazonium chloride and perbromide respectively:[2] iodine gives iodobenzene because of the instability of the diazonium iodide. When heated with hydrochloric acid to 200° in a sealed tube phenylhydrazine is largely converted into p-phenylenediamine together with some aniline and ammonia: $\phi \cdot NH \cdot NH_2 \rightarrow H_2N \cdot C_6H_4 \cdot NH_2$. This apparent rearrangement only takes place at high temperatures, and its mechanism is unknown.

The coupling of phenylhydrazine and its derivatives with the aromatic diazo compounds can take place in two directions according to the conditions. In the presence of mineral acids the diazo compound appears to couple with the primary amino group to give a tetrazene which immediately breaks up to an azide and an amine:

$$\phi \cdot NH \cdot NH_2 + \phi \cdot N_2Cl \longrightarrow \phi \cdot NH \cdot NH \cdot N{:}N \cdot \phi \longrightarrow \phi \cdot NH_2 + \phi \cdot N_3.$$
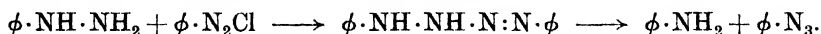
If the benzene rings of the two coupling components contain different substituents, two azides and two amines are formed: in other words the tetrazene appears to be tautomeric, as it may well be, since it contains two triad systems similar to the one in a diazoamino compound (p. 460):

$$\begin{array}{ccc}
Ar \cdot NH \cdot NH \cdot N{:}N \cdot \phi & \rightleftharpoons & Ar \cdot N{:}N \cdot NH \cdot NH \cdot \phi \\
\downarrow & & \downarrow \\
Ar \cdot NH_2 + N_3 \cdot \phi & & Ar \cdot N_3 + H_2N \cdot \phi.
\end{array}$$
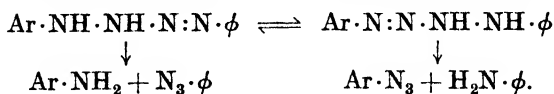
[1] F. D. Chattaway, *J.C.S.* 1907, **91**, 1323; 1908, **93**, 270; 1909, **95**, 1065.
[2] Idem, ibid. 1909, **95**, 864.

In the presence of acetic acid, coupling takes place with the secondary nitrogen atom; the product is an unsymmetrical tetrazene which is more stable and can be isolated (see p. 465):

$$\phi \cdot N_2Cl + \phi \cdot NH \cdot NH_2 \longrightarrow \phi \cdot N:N \cdot N\phi \cdot NH_2.$$
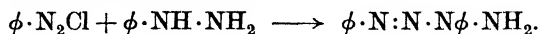
The importance of phenylhydrazine in organic chemistry arises largely from the ease with which it forms crystalline hydrazones with compounds containing a carbonyl group, a reaction which is discussed below. In addition it is used for the synthesis of a variety of heterocyclic compounds. In industry it is used in the manufacture of certain azo dye-stuffs and of drugs of the antipyrine type. Antipyrine itself is prepared by the condensation of phenylhydrazine with acetoacetic ester and methylation of the product:
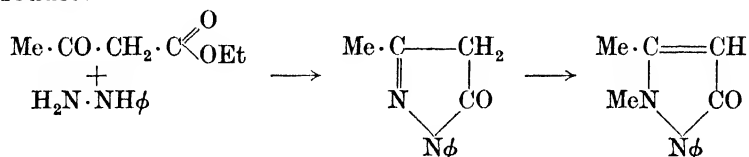
The secondary aryl hydrazines of formula $Ar \cdot NR \cdot NH_2$ are usually obtained by the reduction of nitrosamines, $Ar \cdot NR \cdot NO$, with mild reducing agents (see p. 452). Those containing an alkyl group can be prepared by the alkylation of acetyl hydrazines, followed by hydrolysis:

$$\phi \cdot NH \cdot NH \cdot COCH_3 \longrightarrow \phi \cdot NMe \cdot NH \cdot COCH_3 \longrightarrow \phi \cdot NMe \cdot NH_2:$$
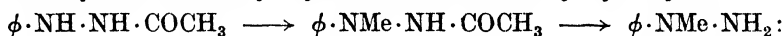
the acetyl group makes the one nitrogen atom so feebly basic that alkylation takes place entirely on the other. These compounds are basic and resemble the N,N-dialkyl hydrazines in their reactions with nitrous acid and oxidizing agents. The diaryl compounds such as N,N-diphenylhydrazine differ from the others in that the bond between the nitrogen atoms is much more easily broken: hydrolysis to ammonia and a hydroxylamine takes place with sulphuric acid at a low temperature,

$$\phi_2N \cdot NH_2 \longrightarrow \phi_2NOH + NH_3,$$
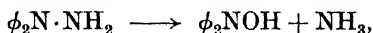
and the hydroxylamine then undergoes further rearrangements.[1] This behaviour is a forecast of the spontaneous dissociation of the tetra-aryl hydrazines.

(2) *The N,N'-Disubstituted Hydrazines or Hydrazo Compounds,* R·NH·NH·R

The main difference between these compounds and the hydrazine derivatives discussed so far lies in their close relationship to the azo compounds, $R \cdot N:N \cdot R$, from which they can be obtained by reduction, and into which they are usually converted by oxidation. The best known and the more interesting members of the group are the aromatic compounds.

The N,N'-dialkyl hydrazines cannot be obtained by alkylation of hydrazine for the reasons given above. They can be prepared by the

[1] H. Wieland and C. Müller, *Ber.* 1913, **46**, 3307.

alkylation of dibenzoylhydrazine followed by hydrolysis with hydrochloric acid:[1]

$$\phi \cdot CO \cdot NH \cdot NH \cdot CO \cdot \phi \longrightarrow \phi \cdot CO \cdot NMe \cdot NMe \cdot CO \cdot \phi \longrightarrow NHMe \cdot NHMe.$$

They are hygroscopic basic liquids like the primary alkylhydrazines. They are readily oxidized to the aliphatic azo compounds, and with nitrous acid give a dinitroso derivative which loses nitric oxide:[2]

$$MeN(NO) \cdot N(NO)Me \longrightarrow MeN:NMe + 2NO.$$

Hydrazoformic ester, $EtO_2C \cdot NH \cdot NH \cdot CO_2Et$, which is often called hydrazodicarboxylic ester, is an N,N'-compound, but, unlike the N,N'-dialkylhydrazines, it can be prepared from chloroformic ester, $Cl \cdot CO_2Et$, and hydrazine, presumably because in the first product formed,

$$EtO_2C \cdot NH \cdot NH_2,$$

the secondary nitrogen atom is less basic than the primary. It is the source of the interesting azodicarboxylic ester (see p. 433), but a vigorous oxidizing agent such as hot nitric acid is needed to effect the oxidation. The ease with which the hydrazo compounds are oxidized to azo compounds varies between wide limits: in the aliphatic series it seems to be the greater the more basic the nitrogen atoms.

The aromatic hydrazo compounds such as hydrazobenzene,

$$\phi \cdot NH \cdot NH \cdot \phi,$$
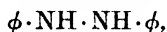
which was first obtained by A. W. Hofmann in 1863, are prepared by the reduction of the aromatic nitro compounds in alkaline solution. The mechanism of their formation has been discussed above (p. 253). They are of importance as dye-stuff intermediates because of their transformation into benzidines from which 'direct' azo dyes can be obtained (see p. 449). They are insoluble in water, dilute acids, and alkalis, and are colourless when pure, but because of the ease with which they are oxidized to azo compounds, they usually turn yellow or reddish on standing in the air. They can also be obtained by the reduction of azo compounds, and this is best done with zinc and alkali or with magnesium and magnesium iodide; in the latter reaction the compound $Ar \cdot N(MgI) \cdot N(MgI) \cdot Ar$ is formed and is decomposed by water to the hydrazo compound.[3] With more vigorous reducing agents the azo compound is reduced to two molecules of an amine, and the hydrazo compounds themselves can be similarly reduced:

$$\phi \cdot NH \cdot NH \cdot \phi \longrightarrow 2\phi \cdot NH_2.$$

The hydrazo compounds behave as di-secondary amines, giving unstable dinitroso compounds, e.g. $\phi \cdot N(NO) \cdot N(NO) \cdot \phi$, with nitrous acid and a diacetyl derivative with acetic anhydride.

The ease with which hydrazobenzene loses hydrogen and passes into azobenzene is remarkable. Weak oxidizing agents suffice and even atmospheric oxygen is effective, especially in the presence of alkali, and in alcohol or benzene an almost quantitative yield of hydrogen peroxide is

[1] T. Folpmers, *Rec. trav. chim.* 1915, **34**, 50.   [2] J. Thiele, *Annalen*, 1910, **376**, 257.

[3] W. E. Bachmann, *J. Amer. C. S.* 1931, **53**, 1524.

produced simultaneously.[1] A more remarkable observation was made by H. Wieland, who found that hydrazobenzene is dehydrogenated by finely divided palladium, some of the hydrogen reducing unchanged hydrazobenzene to aniline, but some of it remaining in the palladium.[2]

Hydrazobenzene and its derivatives cannot be distilled, because on heating mutual oxidation and reduction take place, one molecule being oxidized to the azo compound while another is reduced to two molecules of an aniline:

$$2\phi \cdot NH \cdot NH \cdot \phi \longrightarrow \phi \cdot N:N \cdot \phi + 2\phi \cdot NH_2.$$
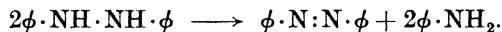
Measurements of the rate of the reaction seem to show that it is monomolecular,[3] and hence the suggestion has been made that the primary step is the dissociation of the hydrazo compound into two free radicals, and this is not unlikely in view of the known dissociation of the tetra-aryl hydrazines. Nevertheless, such a mechanism finds no support in the products which Wieland[4] obtained from the decomposition of unsymmetrical hydrazo compounds. Such a hydrazine would dissociate into two dissimilar radicals which should unite to give two symmetrical azo compounds and one unsymmetrical azo compound.

$$\phi \cdot NH \cdot NH \cdot Ar \left\langle \begin{array}{c} \nearrow \phi \cdot NH \\ \searrow Ar \cdot NH \end{array} \right\langle \begin{array}{c} \nearrow \phi \cdot N:N \cdot \phi \\ \rightarrow \phi \cdot N:N \cdot Ar \\ \searrow Ar \cdot N:N \cdot Ar \end{array}$$
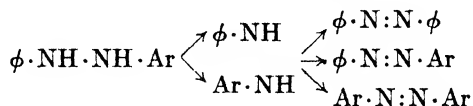
The sole product is, however, the unsymmetrical azo compound.

The most striking reaction of the hydrazo compounds is the transformation they undergo when treated with acids; this is usually called the benzidine change, since with hydrazobenzene itself the chief product is benzidine. In rare cases the reaction takes place on heating the compound alone, but usually the presence of an acid is necessary. This may be a dilute aqueous acid or a hydrogen halide in an inert solvent and sometimes acetic acid alone is sufficient. The products of the change appear to result from a rearrangement of the parts of the molecule and are of four types.

Benzidine

o,p'-Diamino-diphenyl
Diphenyline

$\phi \cdot NH \cdot NH \cdot \phi$

Semidine

o-Semidine
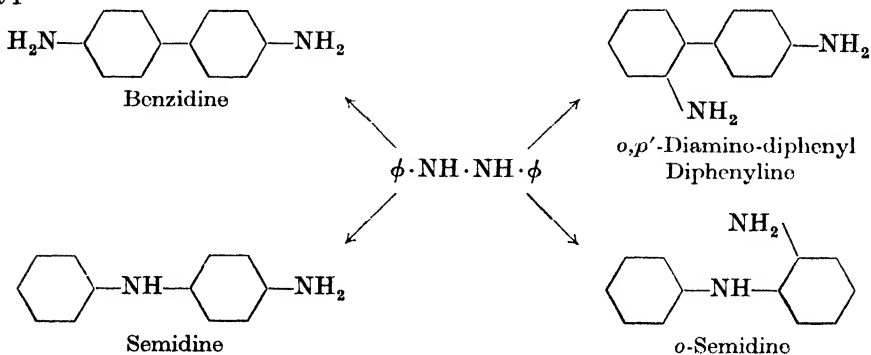
[1] J. H. Walton and G. W. Filson, ibid. 1932, **54**, 3228.
[2] *Ber.* 1912, **45**, 492.
[3] G. O. Curme, *J. Amer. C. S.* 1913, **35**, 1143.   [4] *Ber.* 1915, **48**, 1098.

These types are all the possible ways in which two units $\phi \cdot$NH— can be arranged with ortho-para coupling, with the exception of the o,o'-diamino-diphenyl (ortho-benzidine) which has never been obtained from hydrazobenzene or its simpler derivatives. In the naphthalene series, however, the o,o'-diamines are often formed in good yield. The proportions in which the various products are formed depend on the conditions under which the rearrangement takes place and on the nature and position of the substituents attached to the two rings.[1] With hydrazobenzene itself benzidine is obtained in very good yield. Substituents in the para positions have a great influence, but many groups, such as —Cl, —CO_2H, —SO_3H, and —O$\cdot$$COCH_3$, are ejected during the change: other groups such as —OMe and —NH_2 in the para position are not displaced and so the product is the only possible one, the ortho-semidine. The mechanism of this change is obscure; at one time it was thought that with all compounds of the type $\phi \cdot$NHR there was a tendency for the substituent R to migrate to the ring by a rearrangement taking place inside the molecule, and the benzidine change was considered as two consecutive migrations, first from hydrazobenzene to semidine and then from semidine to benzidine. This view is erroneous, because experiment shows that semidine is unaffected by acids and is not converted into benzidine.[2] Further, many of the apparent rearrangements with which the benzidine change was classified have been shown to be intermolecular reactions and not intramolecular rearrangements. The obvious suggestion as to the mechanism of the reaction is that the molecule of hydrazobenzene dissociates at the N—N link to give two free radical units which combine in various ways. This view seems, however, to be disproved by two facts. Firstly, tetraphenylhydrazine, which is known to dissociate into the free radical ϕ_2N, also undergoes the benzidine change, since it is N,N'-diphenyl-hydrazobenzene; but under the conditions when it is known to be dissociated the benzidine change does not take place.[3] Secondly, if there is dissociation into free radicals, these should be capable of combining not only with identical radicals, but also with similar radicals, so that if two hydrazo compounds distinguished by different substituents undergo the benzidine change in the same solution, there should be a certain amount of a benzidine made up from a radical from one hydrazobenzene and one from the other. This point has been tested with 2,2'-dimethoxyhydrazobenzene and 2,2'-diethoxyhydrazobenzene, in which the substituents are so much alike that great difference in the reactivity of the radicals, if they exist, can hardly affect the issue. Both hydrazobenzenes, however, rearrange independently of the presence of the other, and no benzidine containing one methoxy and one ethoxy group can be found among the products.[4]

[1] This point has been studied in detail by P. Jacobson and his pupils; *Annalen*, 1922, **428**, 76.

[2] R. Robinson and G. M. Robinson, *J.C.S.* 1918, **113**, 645.

[3] H. Wieland and S. Gambarjan, *Ber.* 1906, **39**, 1503.

[4] C. K. Ingold and H. V. Kidd, *J.C.S.* 1933, 984.

Another possible mechanism of the change is that the hydrazo compound is hydrolysed to a phenylhydroxylamine and an aniline, and that the former rearranges to a p-amino-phenol which then condenses with the aniline.

$$\phi\cdot NH\cdot NH\cdot\phi \longrightarrow \phi\cdot NH_2 + \phi\cdot NHOH \longrightarrow \phi\cdot NH_2 + HO\cdot C_6H_4\cdot NH_2$$

$$\longrightarrow \text{benzidine}$$

This is ruled out by the fact that an amino-phenol and an aniline do not condense to give benzidine. The change thus seems to be an intramolecular rearrangement, but there is insufficient evidence to support any definite hypothesis as to its mechanism. In particular the part played by the acid in bringing about the change and the way in which certain substituents in the para position can be ejected during the change await a satisfactory explanation.

In the naphthalene series the benzidine change often results in the formation of an o,o'-diamine, which is never formed from the hydrazobenzenes. These diamines can react further by ring closure to give a pyrrole derivative, so that the latter is sometimes the actual product obtained. Thus when α-hydrazonaphthalene is heated with dilute hydrochloric acid, o,o'-diamino-dinaphthyl is formed; if heated with more concentrated acid, this ortho-benzidine loses ammonia to form 'dinaphthylcarbazole'.[1]

In other cases the intermediate ortho-benzidine cannot be separated. An example is the action of phenylhydrazine on 2,3-hydroxynaphthoic acid.[2] Instead of the substituted hydrazine which would be expected from a naphthol, the product is a carbazole derivative: the hydrazo compound first formed must rearrange to a benzidine, which then loses ammonia to close the indole ring. The interest of these reactions lies in their analogy with Fischer's synthesis of indoles from hydrazones (see p. 498).

Benzidine and some of its simpler derivatives are of technical importance

[1] R. Nietzki and O. Goll, *Ber.* 1885, **18**, 3252.

[2] M. Schöpff, ibid. 1896, **29**, 265.

for the manufacture of 'direct' cotton dyes. They are produced commercially in one process from the nitro compound by reducing it to the hydrazo compound under conditions where the latter at once rearranges.

(3) *The Tri- and Tetra-substituted Hydrazines*

The tri-substituted hydrazines have been little investigated and are not easy to prepare. The only method of preparation which is of any value is the action of a Grignard compound on a nitrosamine. The product should be a hydroxy-hydrazine, but this is reduced immediately by excess of the magnesium compound to the hydrazine.[1]

$$\begin{matrix} \phi \\ \diagdown \\ R \diagup \end{matrix} N \cdot NO + R' \cdot MgBr \longrightarrow \begin{matrix} \phi \\ \diagdown \\ R \diagup \end{matrix} N \cdot N \begin{matrix} \diagup OMgBr \\ \diagdown R' \end{matrix} \longrightarrow \begin{matrix} \phi \\ \diagdown \\ R \diagup \end{matrix} N \cdot NHR'$$

The compounds hardly react with Fehling's solution, but can be oxidized to the tetrazanes which show the interesting property of dissociation into free hydrazyl radicals (see p. 462).

The tetra-arylhydrazines are very remarkable substances which give rise to two distinct types of free radicals. Our knowledge of the group is largely due to H. Wieland and his pupils. They were first made by the action of iodine on the sodium derivatives of the diarylamines,[2]

$$2\phi_2 NNa + I_2 \longrightarrow 2NaI + \phi_2 N \cdot N\phi_2,$$

but are more readily prepared by the oxidation of the diarylamines with lead peroxide in ether or benzene, or with permanganate in acetone.[3]

$$2\phi_2 NH \longrightarrow \phi_2 N \cdot N\phi_2 + H_2O$$

They are crystalline solids which can be kept unchanged in the dark, but decompose fairly rapidly in solution. They can easily be reduced to two molecules of the secondary amine and are not basic in the ordinary sense of the word: their remarkable behaviour towards acids is discussed later. They are unattacked by alkalis.

The instability of these hydrazines in solution arises from their spontaneous dissociation into free radicals which contain divalent nitrogen.[4]

$$Ar_2 N \cdot NAr_2 \rightleftharpoons 2Ar_2 N$$

The influence of the aromatic groups on the bond between the nitrogen atoms is the same as their effect in a compound such as hexaphenylethane, which dissociates into radicals containing trivalent carbon.

$$\phi_3 C \cdot C\phi_3 \rightleftharpoons 2\phi_3 C$$

[1] M. Busch and R. Hobein, *Ber.* 1907, **40**, 2099; H. Wieland and H. Fressel, ibid. 1911, **44**, 901.

[2] F. D. Chattaway and H. Ingle, *J.C.S.* 1895, **67**, 1090.

[3] H. Wieland and S. Gambarjan, *Ber.* 1906, **39**, 1500.

[4] H. Wieland, *Annalen*, 1911, **381**, 212; H. Wieland and H. Lecher, ibid. 1912, **392**, 156.

That dissociation into free radicals takes place is shown by the following facts. The solid tetrarylhydrazines are colourless, but in solution in chloroform or nitrobenzene they are yellow to deep green according to the nature of the substituents present in the rings. The colour deepens on warming and fades again on cooling, and if the solution is diluted, Beer's law is not obeyed: in other words, the total colour seen by looking through the solution as a whole increases on dilution, showing that the amount of coloured compound is a function of the dilution, or the dissociation is greater at high dilution. The effect of substituents on the extent of dissociation is the opposite to that in the triphenylmethyls; in the latter case introduction of negative groups such as —NO_2 increases the dissociation, while with the hydrazines positive substituents, e.g. —OMe and —NMe_2, favour dissociation. With tetra-(p-dimethylamino-phenyl)-hydrazine, $(Me_2N \cdot C_6H_4)_2N \cdot N(C_6H_4 \cdot NMe_2)_2$, the dissociation in solution is so great that it can be measured cryoscopically: a 0·8 per cent. solution in benzene is dissociated into free radicals to an extent of 10 per cent. and in nitrobenzene to an extent of 21 per cent. These solutions are, of course, deeply coloured.[1] It should be noticed that the dissociation on solution or dilution is not instantaneous, but needs several seconds, so that the molecule must have a certain energy of activation before it dissociates.

The chemical behaviour of these hydrazines in solution is clearly the behaviour of the free radicals and not of the undissociated molecule. Unlike triphenylmethyl and its derivatives the radicals do not combine with oxygen, but they react immediately with other free radicals, namely nitric oxide and triphenylmethyl, to give addition products which can be isolated as solids: their formulae are $Ar_2N \cdot NO$ and $Ar_2N \cdot C\phi_3$, respectively, and on heating they dissociate again into their components. The free radicals themselves are not stable and do not resemble radicals such as nitric oxide. If a solution of a tetra-arylhydrazine is allowed to stand, the radicals react and give the diarylamine and the phenazine, two polymerizing and the hydrogen set free reducing two others.

In the various compounds the rate at which this reaction takes place varies with the extent of dissociation and is complete in boiling benzene in 10–30 minutes. This reaction recalls the rather similar behaviour of triphenylmethyl when illuminated.[2]

[1] H. Wieland, *Ber.* 1915, **48**, 1091.
[2] J. Schmidlin and A. Garcia-Banús, ibid. 1912, **45**, 1344.

$$6\phi_3C \longrightarrow 4\phi_3CH + \quad C\phi\!-\!\phi C$$

In the solid form the hydrazines do not dissociate because the energy content is too low to provide the necessary energy of activation, but if at the temperature of liquid air fast-moving electrons are projected on to solid tetraphenylhydrazine, it turns bright green, the colour disappearing when the beam of electrons is shut off.[1]

That the aromatic nuclei must be attached directly to the nitrogen atoms for these phenomena of dissociation to appear is shown by the behaviour of tetrabenzylhydrazine, $(\phi \cdot CH_2)_2N \cdot N(CH_2 \cdot \phi)_2$. This compound can be prepared from dibenzylhydrazine by reducing its benzylidene compound to tribenzylhydrazine and treating this with benzyl bromide.

$$(\phi \cdot CH_2)_2N \cdot NH_2 \longrightarrow (\phi \cdot CH_2)_2N \cdot N : CH \cdot \phi \longrightarrow (\phi \cdot CH_2)_2N \cdot NH \cdot CH_2 \cdot \phi$$
$$\longrightarrow (\phi \cdot CH_2)_2N \cdot N(CH_2 \cdot \phi)_2$$

It is a solid (melting-point 139·5°) and can be distilled unchanged at 260°/32 mm.; it shows no tendency to dissociate whatever and is only reduced to dibenzylamine with difficulty. The reason why this compound does not dissociate and tetraphenylhydrazine does lies in the nature of the free radical. The dissociation of the tetra-arylhydrazines and the hexa-aryl ethanes is not due to any special property of the undissociated compounds; the dissociation is not, for example, the result of a steric effect caused by the close packing of large groups. This point is shown very clearly by the profound changes in the extent of dissociation which can be brought about by introducing substituents in the para position, where steric effects can play no part. The dissociation arises from an increased stability of the free radical itself, and, because dissociation is only observed when there are at least two aromatic groups in the radical, the increase of stability must be due to a lowering of the energy content of the radical through the phenomenon of resonance. The structure of the free radical from tetraphenylhydrazine can be written in seven ways, in each of which a different atom is unsaturated; the actual state of the radical cannot be represented in one formula; it is a resonance-hybrid of these seven structures.

[1] H. Wieland and H. Lecher, *Annalen*, 1911, **381**, 216.

With tetrabenzylhydrazine there is not the same possibility of resonance between a number of different structures, since the nitrogen atom is not directly attached to an aromatic nucleus. Hence there is no increase in the stability of the radical and dissociation does not take place. The effect of substituents on the stability of the radicals is of the same nature as their orientating effect in benzene substitution.[1] This is shown by the behaviour of tetra-(dimethylamino-phenyl)-hydrazine which has been mentioned above. Unlike the other tetra-arylhydrazines it can form a true salt with acids in virtue of the $-NMe_2$ groups which it contains. The free base is largely dissociated into free radicals in solution, but the salts show no sign of such dissociation. This arises from the opposite natures of the uncharged amino group $-NMe_2$ and the kation $-NMe_2H^+$, just as these two groups have the opposite orientating effect in benzene substitution (see p. 69).

The dialkyl-diaryl hydrazines such as $\phi \cdot NMe \cdot NMe \cdot \phi$ can be obtained by loss of nitrogen from the corresponding tetrazene, $\phi \cdot NMe \cdot N : N \cdot NMe \cdot \phi$ (see p. 465). They are oils which show no tendency to dissociate in solution, at 140° they decompose into a secondary amine and an anil.[2]

$$\phi \cdot NEt - NEt \cdot \phi \longrightarrow \phi NHEt + \phi \cdot N : CH \cdot CH_3$$

A further characteristic peculiarity of the tetra-aryl hydrazines is in their reactions with certain acids and with bromine. When these hydrazines were first obtained it was noticed that they do not form ordinary salts, but dissolve in strong sulphuric acid with a deep blue or violet colour. Compounds of the same colour can be obtained by the action of hydrogen chloride or sulphuric acid on the hydrazines dissolved in ether, and bromine gives a similar product. In a few cases the coloured substances can be isolated as solids, but they are very unstable and decompose into a variety of products, which depend on the acid used and the substituents present in the rings. The tetra-p-tolylhydrazines give the most stable coloured salts because the very reactive para position of the aromatic rings is blocked by the methyl group. Wieland, who first investigated these compounds,[3] was of the opinion that the coloured salts were formed by addition of a molecule of, say, hydrogen chloride, but that during the addition the hydrazine rearranged to a quinonoid structure (I). For the bromine complex, which contains three atoms of bromine to one of the hydrazine, he proposed the formula (II) in which two bromine atoms are held together as a kind of perbromide anion:

[1] The nature of the effect has been discussed by C. K. Ingold, *Trans. Faraday Soc.* 1934, **30**, 55.

[2] H. Wieland and H. Fressel, *Annalen*, 1912, **392**, 135.   [3] *Ber.* 1907, **40**, 4263.

Owing to their instability these salts are difficult to investigate, but there is no doubt that they contain the N—N link unbroken, because the hydrazine can be recovered from them by alkalis. During the formation of the chlorides with hydrogen chloride a certain amount of reduction takes place, because the salt is contaminated with a certain amount of di-*p*-tolylamine which must arise from the reduction of the hydrazine.

The true structure of these salts is most probably not that proposed by Wieland but the 'hydrazinium' structure suggested by E. Weitz and H. W. Schwechten.[1] We have already seen that the triarylamines such as triphenylamine behave rather like noble metals, in that they do not react with hydrogen chloride to form a salt, but will combine with a halogen to form a halide in which the kation is a free radical, $[\phi_3N—]^+Hal^-$. The same phenomenon is shown by the tetra-arylhydrazines; they are metallic in the sense that by the loss of one electron a molecule becomes a kation, which is necessarily a free radical, $[Ar_2N—\underset{|}{N}Ar_2]^+$, because it contains an odd number of electrons. The state of one of the nitrogen atoms is the same as in the uncharged free radical formed in the dissociation of a tetra-arylhydrazine: in the latter case the nitrogen has seven electrons in its outer orbit—its original five and one from each of the attached aryl groups; in one nitrogen atom of the hydrazinium kation there are also seven—the original five with three from each of the attached atoms, together with a loss of one which makes it a positively charged ion. From this point of view the occurrence of the hydrazinium ion is not surprising, but is the same phenomenon as the occurrence of an uncharged radical ϕ_2N. Another way of regarding the matter is to think of the radicals $Ar_2N\cdot\underset{|}{N}Ar$ formed in the spontaneous dissociation of the tetrazanes of formula

$$Ar_2N\cdot NAr\cdot NAr\cdot NAr_2$$

the hydrazinium salt $[Ar_2N\cdot NAr_2]X$ is related to this radical just as tetramethylammonium chloride, $[NMe_4]Cl$, is related to trimethylamine, NMe_3.

The evidence upon which this structure of the coloured salts of these hydrazines is based is as follows. Like a metal such as copper, they cannot form a salt with an acid unless there is an oxidizing agent present to take up the hydrogen of the acid. In the absence of any other agent the hydrazine itself can act as an oxidizing agent and is reduced by the hydrogen from the acid to the diarylamine the formation of which has been already mentioned. If an oxidizing agent such as lead peroxide is added, coloured salts are formed immediately, even with acids such as picric and acetic acids. Tetra-*p*-tolylhydrazine further unites immediately with chlorine tetroxide to give the hydrazinium perchlorate $[Ar_2N\cdot NAr_2]^+ClO_4^-$, a dark violet crystalline compound which is more stable than the majority of the coloured salts and can be analysed: this is similar to the direct union of chlorine tetroxide and a metal to give a perchlorate. The addition complex

[1] *Ber.* 1927, **60**, 1203.

with three atoms of bromine which Wieland prepared is clearly the ordinary perbromide, $[Ar_2N \cdot NAr_2]^+Br_3^-$; a large number of organic bases form perbromides rather than bromides, e.g. the diazonium perbromides (p. 403), and these contain the anion Br_3^- and never the Br_2^- which is necessary on Wieland's formula. Finally, the instability of the radicals together with the fact that, unlike triphenylmethyl, they do not combine with molecular oxygen is exactly the same as with the radicals of the type NAr_2. There is a further resemblance between the hydrazinium salt and that of a noble metal in that both are oxidizing agents and can be reduced easily to the hydrazine and the metal, respectively. If a hydrazinium salt is treated in neutral solution with potassium iodide, iodine is immediately liberated and the hydrazine formed:

$$[Ar_2N \cdot NAr_2]X + KI \longrightarrow Ar_2N \cdot NAr_2 + KX + I.$$

(4) *The Hydrazones and Azines*

These compounds may be regarded as the condensation products of the hydrazines with ketones and aldehydes. The azines, which contain the grouping $>C:N \cdot N:C<$, are derivatives of hydrazine itself, while the hydrazones are derived from hydrazine, mono-substituted hydrazines, and di-substituted hydrazines of the general formula $RR'N \cdot NH_2$. The term azine is also used for another group of organic compounds which, among other methods of preparation, are formed by the condensation of an aromatic *o*-diamine with an α-diketone.

To avoid confusion, this latter group are better described as phenazines.

The true hydrazones, i.e. those derived from hydrazine, and the azines will be dealt with first. Most aldehydes condense very readily with hydrazine in the cold to give the azine:

$$2R \cdot CHO + NH_2 \cdot NH_2 \longrightarrow RCH:N \cdot N:CHR.$$

With ketones the ketazine is formed with greater difficulty, and the hydrazone is the usual product:

$$RR'C:O + H_2N \cdot NH_2 \longrightarrow RR'C:N \cdot NH_2.$$

The hydrazones of the aldehydes can be obtained from the azine by heating it with excess of hydrazine hydrate. Both the azines and hydrazones are crystalline solids which can be hydrolysed to hydrazine and the carbonyl compound from which they are derived by boiling with mineral acids. The azines on heating alone are decomposed with loss of nitrogen to give an unsaturated compound, $RCH:N \cdot N:CHR \longrightarrow N_2 + RCH:CHR$, and this reaction is sometimes used for preparing substituted ethylenes. The hydrazones also decompose in the same way but not so easily. The loss of nitrogen takes place more readily in the presence of alkalis, and the

reaction serves as a useful method for reducing a carbonyl group to a methylene group (the Wolff-Kishner reaction).

$$\text{>CO} \longrightarrow \text{>C:N·NH}_2 \longrightarrow \text{>CH}_2 + \text{N}_2$$

The hydrazone can be heated in a sealed tube with sodium ethoxide in absolute alcohol,[1] or sometimes it is more convenient to heat the solid hydrazone with solid caustic alkali.[2] The hydrazones can be oxidized by mercuric oxide to aliphatic diazo compounds, and this is the only method whereby some of these substances can be prepared (see p. 350).

The hydrazones derived from phenylhydrazine, which are often called hydrazones but are more strictly described as phenylhydrazones, are among the most important derivatives of that compound. In 1883 Emil Fischer discovered that phenylhydrazine condenses readily with practically every substance that contains a true carbonyl group (i.e. excluding carboxylic acids, their esters, and amides); and thus, not only can it be used as a reagent for the detection of that group, but the resulting hydrazones serve as reagents for identifying and characterizing ketones and aldehydes, because in most cases they can be easily purified by recrystallization. The structure of a phenylhydrazone is known to be

$\text{>C:N·NH}\phi$ and not the ring $\text{>C}\underset{\text{N}\phi}{\overset{\text{NH}}{\diagdown|}}$ because the N,N-di-substituted

hydrazines, such as methylphenylhydrazine, give hydrazones very similar to the phenylhydrazones, while the N,N'-compounds such as $\phi \cdot \text{NH} \cdot \text{NHMe}$ do not condense with the carbonyl group. The phenylhydrazones are closely related to the azo compounds of formula $\text{RR'CH·N:N·}\phi$ and differ from them in the absence of the typical azo colour. Usually the azo compound changes irreversibly into the hydrazone (see p. 434), and the formation of hydrazones by coupling aromatic diazo compounds with certain aliphatic compounds is mentioned on p. 411.

Phenylhydrazine condenses with aldehydes and ketones much more readily than hydrazine itself. In most cases all that is necessary is to warm the two compounds together in a mixture of acetic acid and water, or in alcoholic or aqueous alcoholic solution. The reaction is reversible, and increase in hydrogen-ion concentration favours the hydrolysis to free phenylhydrazine.[3] The phenylhydrazones are stable crystalline compounds, sparingly soluble in most organic solvents. They are not oxidized by Fehling's solution, unlike the hydrazines which are oxidized by this reagent and evolve all their nitrogen. They can be hydrolysed back to phenylhydrazine and the ketone or aldehyde by boiling with aqueous acids, but if it is desired to recover a carbonyl compound from its hydrazone, it is often better to heat the hydrazone with aqueous pyruvic acid, which displaces the ketone or aldehyde:

$$\text{RR'C:N·NH}\phi + \text{CH}_3 \cdot \text{CO} \cdot \text{CO}_2\text{H} \longrightarrow \text{RR'CO} + \text{CH}_3 \cdot \text{C(CO}_2\text{H):N·NH}\phi.$$

[1] L. Wolff, *Annalen*, 1912, **394**, 86.
[2] N. Kishner, *Zent.* 1911, ii, 363.
[3] E. G. R. Ardagh and J. G. Williams, *J. Amer. C. S.* 1925, **47**, 2976.

Phenylhydrazones can be reduced to substituted hydrazines best by hydrogen in the presence of palladium.

$$RR'C:N \cdot NH\phi \longrightarrow RR'CH \cdot NH \cdot NH\phi$$

More vigorous reducing agents convert them into a mixture of amines, and this provides a useful method for carrying out the change $>CO \longrightarrow >CHNH_2$.

$$RR'C:N \cdot NH\phi \longrightarrow RR'CHNH_2 + H_2N\phi$$

The oxidation of phenylhydrazones to tetrazenes is mentioned below (p. 464). The action of bromine on the phenylhydrazones of the aromatic aldehydes gives a tribromo derivative:[1] two of the bromine atoms enter the ortho and para positions in the ring which is attached to nitrogen and the third replaces the hydrogen atom of the aldehyde group; the latter bromine atom is reactive and a variety of products can be obtained from these ω-bromo compounds.[2]

NH·N:CHAr   NH·N:CBrAr

The conversion of phenylhydrazones into indoles, an interesting and important reaction discovered by Emil Fischer in 1886, takes place in the presence of reagents such as zinc chloride or mineral acids and is discussed later (p. 498).

Although in the majority of cases phenylhydrazine itself is an admirable reagent for the detection and isolation of ketones and aldehydes, for certain compounds some of its substitution products are better. Those which have been most used are the p-nitro compound, the 2,4-dinitro compound, β-naphthyl-hydrazine and to a less extent p-bromophenyl-hydrazine. The hydrazones derived from these substances melt at higher temperatures than the phenylhydrazones themselves and hence are less soluble; they are therefore useful in the case of simple ketones, the phenyl-hydrazones of which crystallize with some difficulty. Thus the phenyl-hydrazone of acetone melts at 26·6° and is usually seen as an oil, while the p-nitrophenylhydrazone forms golden needles melting at 149°. A second advantage of these compounds, and especially of the nitro derivatives, is that they are more weakly basic than phenylhydrazine itself, and the aqueous solutions of their hydrochlorides can be used directly as reagents because of the hydrolysis of the hydrochloride in solution.[3] p-Nitrophenyl-hydrazine can be used for the quantitative determination of acetone in methylated spirit, the hydrazone being simply filtered off and weighed.

The compounds formed by phenylhydrazine with the sugars deserve

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[1] F. D. Chattaway and A. J. Walker, *J.C.S.* 1925, **127**, 975.

[2] e.g. F. D. Chattaway and A. B. Adamson, ibid. 1930, 157.

[3] W. Davies, ibid. 1922, **121**, 715.

special mention because of their importance in the separation and identification of the simple monosaccharoses. The great difficulty which the sugars present is the fact that they are very soluble in water and crystallize extremely slowly or sometimes not at all, so that from an aqueous solution, especially if it contains a mixture of sugars, it is difficult to get anything but a syrup. The majority of simple sugars, which are aldehydes or ketones, form sparingly soluble and well crystalline derivatives with phenylhydrazine and its analogues. The case of glucose will be discussed. This aldohexose combines under carefully controlled conditions with the equivalent of phenylhydrazine to form a phenylhydrazone, in virtue of its aldehyde group. This phenylhydrazone is somewhat soluble in water and is not used for the identification of glucose; it exists in two isomeric forms, one of which seems to be the true hydrazone

$$\phi NH \cdot N : CH \cdot (CHOH)_4 \cdot CH_2OH$$

and the other the cyclic isomer corresponding to the cyclic half-acetal structure of α-glucose itself.[1] If, however, excess of phenylhydrazine is used and the solution, usually in 50 per cent. acetic acid, is warmed, the phenylosazone is formed and this is a sparingly soluble compound. It contains two phenylhydrazine residues and arises from the oxidation by the excess of phenylhydrazine (which is reduced to aniline and ammonia) of the secondary alcoholic group adjacent to the aldehyde group. This becomes a carbonyl group, which then combines with phenylhydrazine:

$$CH_2OH \cdot (CHOH)_3 \cdot CHOH \cdot CH : N \cdot NH\phi$$
$$\longrightarrow \ CH_2OH \cdot (CHOH)_3 \cdot CO \cdot CH : N \cdot NH\phi$$
$$\longrightarrow \ CH_2OH \cdot (CHOH)_3 \cdot C(:N \cdot NH\phi) \cdot CH : N \cdot NH\phi.$$

A similar compound is formed by a ketose, which contains the group $-CO \cdot CH_2OH$; the terminal primary alcoholic group is oxidized and an osazone results. Not only are these compounds used for separating and identifying sugar, but their formation often throws light on the structure of the sugars. For example, glucose and fructose, the one an aldose and the other a ketose, give the same osazone, which is certain evidence that the essentials of their structure are the same, with the exception of the two terminal carbon atoms involved in osazone formation.

Other hydrazines, as well as phenylhydrazine, are useful in sugar chemistry. Methylphenylhydrazine, $\phi NMe \cdot NH_2$, only forms osazones with ketoses and not with aldoses, with which it forms colourless hydrazones. p-Bromophenylhydrazine also has its special uses.[2]

Since hydrazones and osazones resemble the oximes in containing the group $>C=N-$, it is to be expected that those derived from aldehydes and unsymmetrical ketones may exist in two geometrically isomeric forms:

$$
\begin{array}{cc}
R \cdot C \cdot R' & R \cdot C \cdot R' \\
\| & \| \\
N \cdot NH\phi & \phi NH \cdot N
\end{array}
$$

[1] M. Frèrejacque, *C.r.* 1925, **180**, 1210.
[2] E. Fischer and O. Piloty, *Ber.* 1891, **24**, 4221.

A large number of such cases are known.[1] That they are in fact geometrical isomers, and not structural isomers which differ in the position of a hydrogen atom, $>$C:N·NH·ϕ and $>$CH·N:N·ϕ, is shown by the formation of isomers from diphenylhydrazine in which the potentially mobile hydrogen atom is absent. The stereochemistry of these isomeric hydrazones has not been investigated to the same extent as that of the oximes; there is no general reaction of the hydrazones, such as the Beckmann transformation of the oximes, to serve as a method of attack. In isolated cases, however, the configurations of isomeric hydrazones are known. Thus the hydrazones of the phenacylamines occur in two forms (I and II) and one of these condenses readily with aliphatic aldehydes to

$$
\begin{array}{ccc}
\phi\cdot\overset{\displaystyle C}{\underset{\displaystyle N\cdot NH\phi}{\|}}\text{—CH}_2\cdot\text{NHR} & \phi\cdot\overset{\displaystyle C}{\underset{\displaystyle N\text{—}N\phi\text{—}CHR'}{\|}}\text{—CH}_2\cdot\text{NR} & \phi\cdot\overset{\displaystyle C}{\underset{\displaystyle \phi NH\cdot N}{\|}}\text{—CH}_2\cdot\text{NHR} \\
\text{I.} & \text{III.} & \text{II.}
\end{array}
$$

$+ R'\cdot CHO \rightarrow$

a 1,2,4-triazine derivative (III), while from the other no cyclic compound can be obtained.[2] The reaction determines the configurations of the isomers. Another case is the two osazones of benzil, $\phi\cdot CO\cdot CO\cdot\phi$. Three osazones are possible, just as there are three benzildioximes (p. 177), and although in some cases the three are known, only two can be obtained from benzil. On the analogy of the two more stable dioximes of benzil they are probably (IV) and (V). They both form addition products with stannic chloride; with the β-osazone the product contains one molecule of the chloride and one of the osazone, while that from the α-osazone has the same composition but twice the molecular weight.[3] This suggests that the two osazones have the configurations shown (IV and V). In the β-osazone the space arrangement is such that both atoms of nitrogen can form co-ordinate links with one tin atom, and a complex containing one molecule of stannic chloride and one of the osazone can result; this is not possible with the α-osazone.

$$
\begin{array}{ccc}
\phi\cdot\overset{\displaystyle C}{\underset{\displaystyle \phi NH\cdot N \quad N\cdot NH\phi}{\|\qquad\|}}\text{—}\overset{\displaystyle C}{}\cdot\phi & \phi\cdot\overset{\displaystyle C}{\underset{\displaystyle \phi NH\cdot N \quad N\cdot NH\phi}{\|\qquad\|}}\text{—}\overset{\displaystyle C}{}\cdot\phi & \phi\cdot\overset{\displaystyle C}{\underset{\displaystyle N\cdot NH\phi \quad \phi NH\cdot N}{\|\qquad\qquad\qquad\|}}\text{———}\overset{\displaystyle C}{}\cdot\phi \\
& \searrow\text{Sn}\swarrow & \\
& \text{Cl}_4 & \\
\text{IV. }\beta\text{-osazone} & & \text{V. }\alpha\text{-osazone}
\end{array}
$$

$\longrightarrow$

The phenylhydrazone of acetaldehyde can be obtained in two forms (α-form, melting-point 98°; β-form, melting-point 56°) which are probably geometrical isomers. The two forms differ widely in volatility, the α-form boiling at 236°/20 mm. and the β-form a hundred degrees lower, and can be separated to some extent by distillation under reduced pressure. They

[1] An excellent discussion of this subject will be found in an article by J. Meisenheimer and W. Theilacker, *Stereochemie*, ed. Freudenberg, Leipzig, 1933, p. 1095.

[2] M. Busch, G. Friedenberger and W. Tischbein, *Ber.* 1924, **57**, 1785.

[3] W. Hieber and F. Sonnenkalb, *Annalen*, 1927, **456**, 86.

form a continuous series of solid solutions and there is no means of distinguishing between them by chemical methods. The most surprising behaviour of these isomers is that, to judge by th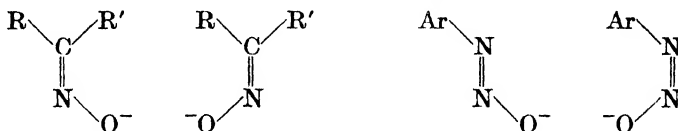e melting-points, the α-form is completely converted into the β- by traces of acids and the β-form partly into the α- by traces of alkalis.[1]

The compound formed from phenylhydrazine and acetoacetic ester does not seem to be a true hydrazone because of the ease with which it is oxidized to benzene-azo-crotonic ester (VI). When heated it loses alcohol and forms phenylmethylpyrazolone (VII).

$$
\begin{array}{ccc}
\underset{\substack{|\\ \text{N}:\text{N}\cdot\phi}}{\text{Me}\cdot\text{C}:\text{CH}\cdot\text{CO}_2\text{Et}} & \longleftarrow \quad \underset{\substack{|\\ \text{NH}\cdot\text{NH}\cdot\phi}}{\text{Me}\cdot\text{C}:\text{CH}\cdot\text{CO}_2\text{Et}} \quad \longrightarrow & \underset{\substack{|\\ \text{NH}-\text{N}\phi}}{\text{Me}\cdot\text{C}=\!\!=\!\!\text{CH}}\!\!\!\!>\!\!\text{CO} \\
\text{VI.} & & \text{VII.}
\end{array}
$$

If the latter is treated with methyl iodide, the N-methyl compound is formed, and this is antipyrin which is extremely useful in medicine. The ring closure to a pyrazole derivative is only one example of the many reactions of hydrazones which lead to heterocyclic systems of various types.

(5) *The Acyl Derivatives of the Hydrazines*

The acid hydrazides of general formula $R\cdot CO\cdot NH\cdot NH_2$ correspond to the amides $R\cdot CO\cdot NH_2$ (Chapter V) which they resemble in many ways. They can be obtained by many of the methods by which an amide is prepared if ammonia is replaced by hydrazine; e.g. from the hydrazine salts of carboxylic acids, and by the action of hydrazine on acid chlorides, esters, and anhydrides. They are also formed by heating an amide with hydrazine when the more volatile ammonia is displaced, and by the action of sodium hypochlorite on the acyl ureas (the simple ureides).[2] The latter reaction is similar to Hofmann's reaction with the amides.

$$R\cdot CO\cdot NH_2 \longrightarrow R\cdot NH_2$$
$$R\cdot CO\cdot NH\cdot CONH_2 \longrightarrow R\cdot CO\cdot NH\cdot NH_2$$

In addition to these hydrazides, diacyl derivatives of hydrazine of the formula $R\cdot CO\cdot NH\cdot NH\cdot CO\cdot R$ are readily obtained either by the action of excess of an agent such as an acid chloride on hydrazine, or from the primary hydrazides by oxidation with iodine, or sometimes by heating alone:

$$2R\cdot CO\cdot NH\cdot NH_2 + 4I \longrightarrow R\cdot CO\cdot NH\cdot NH\cdot CO\cdot R + N_2 + 4HI$$
$$2R\cdot CO\cdot NH\cdot NH_2 \longrightarrow R\cdot CO\cdot NH\cdot NH\cdot CO\cdot R + NH_2\cdot NH_2.$$

The hydrazides resemble the amides in their physical properties and solubilities, but are more resistant to hydrolysis. The primary compounds reduce Fehling's solution and ammoniacal silver solutions like true hydrazines and on treatment with nitrous acid are converted into azides: $R\cdot CO\cdot NH\cdot NH_2 \longrightarrow R\cdot CO\cdot N_3$. From both classes of compounds a

[1] G. Lockemann and O. Liesche, *Annalen*, 1905, **342**, 14; E. G. Laws and N. V. Sidgwick, *J.C.S.* 1911, **99**, 2085.　　　　　[2] P. Schestakov, *Ber.* 1912, **45**, 3273.

large variety of heterocyclic substances can be obtained. The primary compounds contain the group —NH_2 and combine readily with aldehydes and ketones to give hydrazones, and certain of them are useful reagents. The most important example is semicarbazide, a hydrazine derivative of urea which has been discussed above (p. 287). Another interesting example is the hydrazide of d-citronellic acid: this is easily obtained by heating hydrazine with the acid, which results from the gentle oxidation of d-citronellal, and it forms hydrazones very readily. It can be used for the optical resolution of ketones and aldehydes.[1]

Phenylhydrazine gives rise to two series of monoacyl derivatives because the two nitrogen atoms are not identical. The so-called α-compounds, of the formula $\phi \cdot N(CO \cdot R) \cdot NH_2$, are best made by the action of sodamide on the N-chloranilides:[2]

$$R \cdot CO \cdot N\phi Cl + NaNH_2 \longrightarrow RCO \cdot N\phi \cdot NH_2.$$

They can also be obtained by the interaction of an acid chloride or anhydride and the sodium derivative of phenylhydrazine, $\phi NNa \cdot NH_2$. The β-compounds, $\phi \cdot NH \cdot NH \cdot CO \cdot R$, are the product of the direct action of acid chlorides, anhydrides, or amides on phenylhydrazine. In many cases the acids themselves react quite readily with phenylhydrazine to give the phenylhydrazide. This is particularly marked in the case of hydroxy-acids which exist as lactones in the free state; the lactone ring is opened and the hydrazide is formed. For this reason phenylhydrazine is used for the separation of the acids which result from the oxidation of the sugars.[3] If one of these acids in an impure form is heated in 50 per cent. acetic acid with excess of phenylhydrazine, the phenylhydrazide crystallizes out on cooling. The acid or its lactone can be recovered by hydrolysing the hydrazide with baryta, extracting the phenylhydrazine with ether, and precipitating the baryta with its equivalent of sulphuric acid. The solution then contains nothing but the hydroxy-acid.

The term hydrazidine has been applied to two distinct classes of substances. Both are analogous to the amidines (p. 155), and resemble them in being basic; in one class one ammonia residue has been replaced by hydrazine, and in the other both have been replaced. The general formula of one class is $R \cdot C \underset{NH \cdot NHR}{\overset{NH}{<}}$ (which is tautomeric with $R \cdot C \underset{N \cdot NHR}{\overset{NH_2}{<}}$), and of the other $R \cdot C \underset{NH \cdot NHR}{\overset{N \cdot NHR}{<}}$. The former class are more correctly described as amidrazones: the term hydrazidine should be restricted to the compounds which contain two hydrazine residues.[4] Both classes of compounds can be obtained by the action of hydrazines on the imino-ethers (p. 154). Their chief interest lies in the ring closures they undergo to give heterocyclic compounds.

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[1] S. Sabetay, *C.r.* 1930, **190**, 1016.   [2] W. F. Short, *J.C.S.* 1921, **119**, 1445.
[3] E. Fischer and F. Passmore, *Ber.* 1889, **22**, 2728.
[4] See Beilstein, 4th ed., vol. ix, p. 328, footnote.

THE AROMATIC DIAZO COMPOUNDS[1]

IN the aromatic diazo compounds the characteristic group consists of two nitrogen atoms which have replaced one hydrogen atom of a cyclic aromatic system. The group shows both basic and acidic properties, in that salts of the general formula $[\text{Ar} \cdot \text{N}_2]^+ \text{X}^-$ are formed with acids, and also of the formula $[\text{Ar} \cdot \text{N}_2 \cdot \text{O}^-] \text{Na}^+$ with bases. In addition there are non-ionized derivatives such as the diazo cyanides $\text{Ar} \cdot \text{N}_2 \cdot \text{CN}$. In certain of their reactions the compounds resemble the aliphatic diazo compounds (Chap. XI) in which a group of two nitrogen atoms replaces two hydrogen atoms attached to one carbon atom, but they differ profoundly from the azo compounds (Chap. XIV) where two linked nitrogen atoms are attached to two different carbon atoms as in azobenzene, $\phi \cdot \text{N} : \text{N} \cdot \phi$. With the exception of one or two extremely unstable compounds, diazo compounds of the aromatic type are not found in the aliphatic series.

The first aromatic diazo compound to be prepared was obtained in Marburg by Peter Griess in 1858, during the course of an investigation suggested to him by Kolbe. As Griess continued his work, first as A. W. Hofmann's assistant at the Royal College of Chemistry in London and then in the laboratory of Allsopp's Brewery in Burton-on-Trent,[2] the importance of the whole class of compounds became apparent and they attracted wide attention. Their properties and main reactions were rapidly explored and by 1863 azo dye-stuffs derived from them were being manufactured and sold. They have contributed to the progress of chemistry in a variety of ways; not only do they provide a route for preparing compounds of the most diverse natures both in the laboratory and in the factory, but the controversies on the subject of their constitution which have taken place at intervals ever since their discovery have been the means of extending fundamental knowledge and clarifying chemical theory. This very complicated question of constitution, which involves both tautomerism and stereoisomerism, is discussed in detail below. For the moment it will be assumed that in the presence of strong acids the diazo compounds exist as the kations of a strong base $[\text{Ar} \cdot \text{N}_2]\text{OH}$, the diazonium salts, and in alkaline solution as the anions of the weak acid $\text{Ar} \cdot \text{N} : \text{N} \cdot \text{OH}$, the diazotates. They are for the most part unstable compounds which decompose readily both in the solid state and in solution, and are extremely reactive.

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[1] Useful monographs, especially since they represent two different points of view, are *Die Diazo Verbindungen*, A. Hantzsch and G. Reddelien, Berlin, 1921; *The Aromatic Diazo-compounds and their technical applications*, K. H. Saunders, London, 1936.

[2] See the sympathetic obituary notice of Griess by Hofmann, *Ber.* 1891, **24**, Ref. 1007; Griess, who had little time, used to send samples of his preparations to Germany for analysis, accompanied by a barrel of pale ale.

The most important method of preparation is by the action of nitrous acid on primary aromatic amines in the presence of a strong acid:

$$Ar \cdot NH_2 + ONOH + HCl \longrightarrow [Ar \cdot N_2]Cl + 2H_2O.$$

The diazonium salts are freely soluble in water and decompose if the solution is warmed or left to stand. Hence if it is desired to obtain the compound as a solid, it must be prepared under conditions where it will crystallize out, and in the absence of inorganic salts such as sodium chloride or sulphate, which resemble the diazonium salts in their solubilities and will crystallize with them. This may be done in several ways. Nitrous fumes, obtained from the action of nitric acid on starch or arsenious oxide, can be passed into a paste of a salt of the amine with a little water, the whole being cooled with ice. A solution of the diazonium salt is obtained from which the solid salt can be precipitated by the addition of alcohol and ether. This was the method Griess used in the first preparation of a diazo compound. Alternatively, a solution of the amine in dilute sulphuric acid can be treated with barium nitrite, the barium sulphate removed by filtration, and the diazonium salt precipitated with alcohol and ether. Amyl nitrite can be used in non-aqueous solvents as a source of nitrous acid because of the ease with which it breaks up in the presence of acids. An almost quantitative yield of the solid diazonium compound is obtained by dissolving or suspending the amine salt in glacial acetic acid, cooling below 10°, adding a slight excess of amyl nitrite and precipitating with ether.[1]

A modification is to replace the amyl nitrite by methyl or ethyl nitrite; these gaseous nitrites can be obtained by the action of sodium nitrite and dilute sulphuric acid on the alcohol, and, after drying, are passed into the amine solution.

In the vast majority of cases, however, there is no need to separate the explosive solid diazonium salt: an aqueous solution of the compound can be obtained and used for the desired reaction. Hence by far the commonest method is to add sodium nitrite either in aqueous solution or as a solid to a solution of an amine in an aqueous mineral acid; but precautions must be observed. Firstly, excess of mineral acid must be present over and above the amount needed to form the salt of the amine and to decompose the sodium nitrite. This is because the diazo compound can react with the free amine (see below), and since the aromatic amines are not strong bases, a certain amount of free amine will be produced by salt-hydrolysis unless an excess of acid is present. Normally each equivalent of amine needs $2\frac{1}{2}$–3 equivalents of acid, but where the amine is a very weak base, e.g. polynitro- and poly-halogen-substituted anilines, much more is necessary, and sometimes the mixture of sulphuric acid and water corresponding to the monohydrate, H_2SO_4, H_2O, is used. Secondly, the diazo compounds are stable only at a low temperature and the reaction is exothermic; hence the temperature needs regulation. The ordinary rule

[1] A. Hantzsch and E. Jochem, *Ber.* 1901, 34, 3337.

is to cool the solution of the salt of the amine initially to 0–5° and to keep the temperature below 10° during the diazotization and until the diazo compound is used. Some amines, however, such as the naphthylamines and nitroanilines, give more stable diazo compounds and are better diazotized at room temperature, when the reaction proceeds more rapidly. If the amine salt is only sparingly soluble in water, it can be suspended in the acid in a state of fine division, and it passes into solution as the soluble diazonium salt is formed. In such cases the rate of reaction may be quite small. A variety of methods have been used for insoluble and feebly basic amines such as 2,6-dichloro-4-nitroaniline; one way is to dissolve the base in cold concentrated nitric acid and add potassium pyrosulphite (the so-called 'potassium metabisulphite', $K_2S_2O_5$) which reduces some of the nitric acid to nitrous acid *in situ*.[1]

The velocity of diazotization in aqueous solution can be followed if the solution is dilute, and has been measured by various methods. One of the most accurate is to remove samples at measured intervals of time and allow the diazo compound to couple in alkaline solution with some suitable phenol to a soluble azo dye which can be estimated colorimetrically.[2] The reaction is independent of the concentration of the mineral acid when enough is present to convert the amine into its salt. It is bimolecular and involves one molecule of the amine kation and one of undissociated nitrous acid. The rate of reaction is about the same for aniline and its homologues but is much increased when substituents such as $-NO_2,-SO_3H$, and $-Cl$ are present, particularly if they are in the ortho position to the amino group. It is also these substituents which increase the stability of the diazonium salt.

Other reactions in which diazo compounds are formed are known; they are of little practical importance for preparing the compounds, but some are of great interest from the point of view of their structure. The following may be mentioned:

(i) Phenylhydrazine salts can be oxidized in aqueous solution to benzene diazonium salts by a variety of reagents, such as mercuric oxide, mercuric acetate, and nitrous acid:

$$\phi \cdot NH \cdot NH_2, HX + 2O \longrightarrow \phi \cdot N_2X + 2H_2O.$$

(ii) Phenylhydrazine, if treated in alcohol with chlorine or bromine at a low temperature, gives the benzene diazonium halide.[3] This is a good way of obtaining the solid diazonium salt, which can be precipitated by adding ether.

(iii) Nitrosobenzene is converted into benzene diazonium nitrate by the action of nitric oxide.[4]

$$\phi \cdot NO + 2NO \longrightarrow \phi \cdot N_2NO_3$$

[1] O. N. Witt, *Ber.* 1909, **42**, 2953.

[2] J. Böeseken, W. F. Brandsma and H. A. J. Schoutissen, *Proc. K. Akad. Wetensch. Amsterdam*, 1920, **23**, 249, where a discussion of the accuracy of the various methods will be found; J. Reilly and P. J. Drumm, *J.C.S.* 1935, 871.

[3] F. D. Chattaway, ibid. 1908, **93**, 854.   [4] E. Bamberger, *Ber.* 1897, **30**, 512.

With hydroxylamine in alkaline solution it gives the diazotate:[1]

$$\phi \cdot NO + H_2NOH + NaOH \longrightarrow \phi \cdot N_2 \cdot ONa + 2H_2O.$$

As there is no need, as a rule, to isolate diazonium salts for preparative purposes, comparatively little is known about their physical properties, considering that almost every primary aromatic amine which has been described has been diazotized. The physical properties of the simpler derivatives are, however, fairly well known in spite of their instability, thanks to the work of Griess and of Hantzsch and his pupils. The majority of the benzene diazonium salts of the mineral acids are colourless crystalline solids very easily soluble in water, less so in alcohol, and scarcely soluble in ether. They are the salts of a strong base and are not hydrolysed in solution, as is shown by the neutral reaction of the chloride and bromide, and by their conductivities at high dilution. In the solid state many of them, particularly the nitrates, are extremely dangerous compounds, detonating violently when heated and sometimes when rubbed. Bamberger[2] gives a graphic description of an explosion resulting in serious physical injury, which took place when 20 grams of dry p-nitrobenzene diazonium nitrate were spread on a porous plate with a porcelain spatula. When wet the salts are considerably more stable, but moist benzene diazonium perchlorate has been known to explode when rubbed. They resemble the salts of the heavier alkali metals caesium and rubidium in forming a sparingly soluble perchlorate and in the fact that the halides combine with the halogens to give perhalides which are not very soluble in water. The perbromide, $[\phi \cdot N_2]Br_3$, is readily obtained, is comparatively stable, and can be handled without danger. Since it is formed by the action of excess of bromine on phenylhydrazine, it has been suggested that it is tri-N-bromophenylhydrazine, $\phi \cdot NBr \cdot NBr_2$. Its formation from phenyl-hydrazine, however, arises from an initial reaction to produce a diazonium bromide followed by union with more bromine to the perbromide. The perbromide resembles the perhalides of the alkali metals and in solution behaves as a mixture of the bromide with bromine: thus cinnamic acid or its ester gives with the perbromide the dibromo addition product and the diazonium bromide. Many double salts containing a diazonium kation are known and some of these are of technical importance. As is described later, diazo compounds are used for dyeing fabrics with the so-called 'ice colours', and it is clearly of advantage to supply the dyers with a ready-made stable diazo compound, and so avoid the preparation of the diazo solution in the dye-works. Examples of the compounds which have been used for this purpose are the double salts formed by the diazonium salt of a sulphonic acid of naphthalene or the naphthols with the corresponding sodium salt of the same acid. The diazonium compounds derived from the amino-carboxylic and sulphonic acids of benzene occupy a special position because there is a strongly basic group and an acidic group in the same molecule, so that the diazonium compounds exist as internal salts or

[1] Idem, ibid. 1895, 28, 1218.   [2] Ibid. 538.

zwitterions of the betaine type. Thus anthranilic acid gives the diazonium compound (I) and sulphanilic acid gives (II).

I. [structure: benzene ring with N_2^+ and CO_2^- substituents]

II. [structure: benzene ring with N_2^+ and SO_3^- substituents]

These compounds are water soluble, but the solutions naturally show no electrolytic conductivity, although the compounds are salts.

The chemical reactions of the aromatic diazo compounds can be divided into two main classes, those in which the two nitrogen atoms of the diazo group are lost and evolved as gaseous nitrogen, and those in which they remain in the molecule.

In the reactions of the first class the diazo group is replaced by some other group, and since a large variety of groups can be introduced in this way, it is these reactions which give the diazo compounds their great importance for preparative purposes. They serve as valuable intermediates for obtaining many classes of compounds; an aromatic compound can be nitrated and the nitro compound reduced to the primary amine, which is diazotized. The desired group can then be introduced, and in most cases there is no need to isolate the diazo compound. Only the simpler examples of the reactions of this first class will be discussed.[1]

Replacement by hydroxyl. This occurs in most cases very simply by warming the aqueous solution of the diazonium salt or leaving it to stand at room temperature. The product is, of course, a phenol:

$$\phi \cdot N_2Cl + H_2O \longrightarrow \phi \cdot OH + N_2 + HCl.$$

The yield of phenol is often small because of side reactions between the phenol and the undecomposed diazonium salt. The solution must be strongly acid in order to avoid the coupling reaction between phenol and diazo compound which is discussed below, and it is sometimes advisable to blow steam through the reaction mixture and so remove the phenol as it is formed. A solution of the diazonium nitrate should not be used because the nitric acid may attack the phenol which is very readily nitrated. A useful modification of the method, which often gives much better yields of the phenol, is to drop the solution of the diazonium salt slowly into a boiling saturated solution of copper sulphate. The velocity of the reaction can be followed by measuring the volume of nitrogen evolved, and in the substituted compounds it varies enormously with the nature of the substituents.[2] In general it can be said that the methyl substituted compounds decompose a little faster than benzene diazonium salts, and that the nitro-, chloro-, and alkoxy compounds decompose very much more slowly. The reaction is one of the diazonium kation and is independent of the con-

[1] For a discussion of the decomposition reactions of the aromatic diazo compounds see W. A. Waters, *J.C.S.* 1942, 266.

[2] J. C. Cain and F. Nicoll, ibid. 1902, 81, 1412.

centration of mineral acid. To obtain the phenol from these very stable compounds, it is often necessary to heat with moderately concentrated sulphuric acid to 140°.

Replacement by alkoxyl. If a diazonium compound is heated with alcohol the normal product is a phenolic ether,

$$Ar \cdot N_2X + EtOH \longrightarrow Ar \cdot OEt + N_2 + HX,$$

but at the same time another reaction often takes place which results in the replacement of the diazo group by hydrogen, the alcohol being oxidized to the aldehyde:

$$Ar \cdot N_2Cl + CH_3 \cdot CH_2OH \longrightarrow Ar \cdot H + N_2 + HCl + CH_3 \cdot CHO.$$

If there are negative substituents such as $-NO_2$ in the diazo compound, the second reaction predominates, especially if the negative group is in the ortho position. Alteration of the physical conditions can affect the balance between the two reactions: thus methyl alcohol and diazobenzene sulphonic acid under diminished pressure give only benzene sulphonic acid, but under thirty atmospheres pressure only anisole-sulphonic acid is produced. At atmospheric pressure a mixture of the two products is formed.[1]

Replacement by hydrogen can be brought about in other ways. The action of certain reducing agents has this effect, such as formic acid, hypophosphorous acid, and sodium stannite (alkaline stannous chloride). It is possible that the unstable diimine is first formed and rapidly loses nitrogen:[2]

$$Ar \cdot N_2X \longrightarrow Ar \cdot N{:}NH \longrightarrow Ar \cdot H + N_2.$$

Another method is to reduce the diazonium compound to the hydrazine (see p. 380) and oxidize this with copper sulphate or ferric chloride:

$$Ar \cdot N_2X \longrightarrow Ar \cdot NH \cdot NH_2 \longrightarrow Ar \cdot H + N_2 + H_2O.$$

Reactions of this kind are often extremely useful for the purpose of preparing substituted benzene compounds in which the substituents are in positions which they would not take up on direct substitution. The amino group can first be introduced via the nitro compound and can be used to direct the substituent to the desired position. Finally, the amino group can be eliminated by diazotization followed by one of these reactions. An example is the preparation of *m*-nitrotoluene. The methyl group is an

[1] W. B. Shober, *Amer. Chem. J.* 1893, **15**, 379.

[2] S. Goldschmidt, *Ber.* 1913, **46**, 1529.

ortho-para directing group, so that by direct nitration of toluene the *m*-nitro compound is only formed in extremely small amount. If, however, *p*-nitrotoluene obtained by direct nitration is reduced to *p*-toluidine, the acetyl derivative of the latter gives acetyl 3-nitro-4-acetylamino-toluene on nitration, and by hydrolysing off the acetyl group and diazotizing the resulting amine in alcohol *m*-nitrotoluene can be obtained.

Replacement by halogens. The introduction of iodine is different from that of chlorine or bromine because of the exceptional properties of the diazonium iodides. If a solution of a diazonium chloride or sulphate is mixed with one of potassium iodide, nitrogen immediately begins to be evolved and the iodo compound separates:

$$[Ar \cdot N_2]I \longrightarrow Ar \cdot I + N_2.$$

The diazonium iodides themselves are unknown. If the mixing is carried out at a low temperature, yellow crystals sometimes separate which are insoluble in ether. These may be the iodide, but they lose nitrogen rapidly. It is possible that this characteristic instability of the iodide, as compared with the chloride and bromide, is due to a difference in constitution, a point which is mentioned later.

The other halogens cannot be introduced by such simple means, since direct decomposition of the diazonium chlorides and bromides to the chloro or bromo compound only takes place to a minute extent. Of the several methods which are known the more important are those of Sandmeyer and Gattermann. The former consists in adding the diazo solution to cuprous chloride or bromide dissolved in the corresponding acid. A double salt containing copper and the diazo compound is formed which often separates out at room temperature; its composition in the case of benzene diazonium chloride is $2pN_2Cl + Cu_2Cl_2$. This salt on standing or heating breaks up to the chloro compound, nitrogen, and cuprous chloride. The reaction is often carried out by running the diazo solution into the hot cuprous solution when the decomposition is immediate. The yield is often better by this procedure, because the double salt slowly decomposes in another direction on standing in the cold, the copper being oxidized to the cupric state:[1]

$$2\phi \cdot N_2Cl + Cu_2Cl_2 \longrightarrow \phi \cdot N:N \cdot \phi + N_2 + 2CuCl_2.$$

In the double salt the diazo nitrogen is probably co-ordinated to the copper and it seems that this alters the type of decomposition. Gattermann's reaction consists in treating a solution of a diazonium chloride or bromide at room temperature with finely divided copper (the 'copper-bronze' of

[1] H. Erdmann, *Annalen*, 1893, **272**, 141.

commerce can be used). By some catalytic action whose nature is not understood, decomposition into chloro or bromo compound and nitrogen takes place, instead of the normal decomposition into phenol and nitrogen. The method sometimes gives better yields than Sandmeyer's. These methods cannot be used for replacing the diazo group by fluorine. To obtain fluoro compounds the usual way is to couple the diazo compound with a secondary amine—an aliphatic amine such as piperidine is best because no amino-azo compound can be formed—and to decompose the resulting diazoamino compound with concentrated hydrofluoric acid:

$$Ar \cdot N_2Cl + HNC_5H_{10} \longrightarrow Ar \cdot N{:}N \cdot NC_5H_{10} \xrightarrow{HF} Ar \cdot F + N_2 + C_5H_{10}NH, HF.$$

A better method is to precipitate the sparingly soluble borofluoride, $[ArN_2]BF_4$, by adding borofluoric acid to the diazonium solution. The dry salt when heated decomposes smoothly into boron trifluoride and the fluoro-compound.[1]

Replacement by cyanogen. Since the cyano group can be hydrolysed to the carboxyl group (p. 312), this replacement provides a means of preparing aromatic carboxylic acids. It can be achieved by Sandmeyer's reaction, the diazo solution being added to a solution of cuprous cyanide in potassium cyanide. A complex containing copper separates and decomposes on warming. The yields are usually quite good, but in some cases are improved by substituting nickel cyanide, $Ni(CN)_2$, for cuprous cyanide. The reaction is specific for copper and nickel: the cyanides of iron, chromium, zinc, and other metals are useless.[2] The *thiocyanate radical*, —SCN, can be introduced in a similar way by the use of cuprous thiocyanate, but in this case the thiocyanates of cobalt and iron give much better yields.

Groups containing sulphur can be linked to the aromatic ring in various ways and the processes are of technical interest because they give intermediates for some of the sulphur-containing dye-stuffs. One way is to treat the diazonium compound with potassium xanthogenate (potassium ethyl dithiocarbonate, $KS \cdot CS \cdot OEt$). The aryl xanthogenate is formed with loss of nitrogen,

$$Ar \cdot N_2Cl + KS \cdot CS \cdot OEt \longrightarrow Ar \cdot S \cdot CS \cdot OEt,$$

and this can either be hydrolysed to the thiophenol, $Ar \cdot SH$, or heated alone to give the thio-ether, $Ar \cdot SEt$, and carbon oxysulphide.

Replacement by the nitro group. In most cases this reaction is unnecessary since the diazo compound is obtained from the nitro compound through the amine and not vice versa. Some nitro compounds, however, cannot be obtained by direct nitration, and an indirect method of preparation is useful. An example is β-nitro-naphthalene. This compound is not formed when naphthalene is nitrated, but sulphonation of naphthalene under the appropriate conditions gives naphthalene β-sulphonic acid, which can be converted through β-naphthol into β-naphthylamine (see p. 48). If the

[1] G. Balz and G. Schiemann, *Ber.* 1927, **60**, 1186.

[2] A. Korczynski and B. Fandrich, *C.r.* 1926, **183**, 421.

diazo solution derived from this amine is treated with the equivalent of nitrous acid in presence of finely divided cuprous oxide, β-nitro-naphthalene is formed.

The reactions which have been described by no means exhaust the list of groups which can replace the diazo group in reactions of this class. The only other example which will be mentioned is the formation of a C—C link in the decomposition of a diazo compound. It is only aromatic or unsaturated groups that can be introduced; there is no method known by which, for example, benzenediazonium chloride can be converted into toluene. The ease with which the C—C link is formed varies very much with the nature of the substituents present and the nature of the product. In some cases addition of cuprous chloride does not lead to a normal Sandmeyer product but to a diphenyl; thus m-nitrobenzenediazonium chloride with cuprous chloride in the cold gives 87 per cent. of the theoretical amount of 3,3'-dinitrodiphenyl.[1]

If the formation of the C—C link produces a new aromatic structure, the reaction takes place very easily either with copper powder, or without any catalyst in alkaline solution. The best example is R. Pschorr's synthesis of phenanthrene-9-carboxylic acid by the decomposition of diazotized o-amino-α-phenyl-cinnamic acid.[2]

In reactions of this kind the arrangement of the groups attached to the ethylenic double bond is of importance. The more stable geometrical isomer of o-amino-phenyl-cinnamic acid has the *cis* configuration, so that both phenyl rings lie on the same side of the double bond, and the ring closure to the phenanthrene can take place. In the absence of the carboxyl group the more stable isomer is the *trans* compound and this cannot be converted into phenanthrene; the latter can, however, be obtained from the less stable *cis* isomer.[3]

Before discussing the reactions in which the diazo group is not eliminated as gaseous nitrogen, it will be convenient to mention the nature of the products obtained by the action of alkalis on the diazonium salts. The

[1] F. Ullmann and L. Frentzel, *Ber.* 1905, **38**, 726.
[2] Ibid. 1896, **29**, 496.
[3] T. W. J. Taylor and P. M. Hobson, *J.C.S.* 1936, 181.

diazonium hydroxides, $[Ar \cdot N_2]OH$, which might be formed by the action of caustic soda or silver oxide on a solution of a diazonium chloride, are not known, except possibly in very dilute solutions which show the same light-absorption as those of the salt.[1] The first product is a diazotate, i.e. a salt in which the diazo compound forms the anion; as we shall see later, its structure is $[Ar \cdot N:N \cdot O]Na$. The acid from which this salt is derived would be $Ar \cdot N:N \cdot OH$ and is called the normal diazohydrate, but the compounds are not known in the solid state and hardly known in solution, because in most cases they decompose very readily into a phenol and nitrogen. In the presence of mineral acid they are reconverted into the diazonium salt. In some cases, e.g. the p-chloro compound, the addition of acetic acid to a sodium diazotate gives, as Bamberger discovered, the so-called diazo-anhydride, a confusing name because Wolff used it for another class of compounds (see p. 362). They appear to be formed by loss of water between two molecules of the diazohydrate and have been allotted the formula $Ar \cdot N:N \cdot O \cdot N:N \cdot Ar$. They are, however, extremely explosive and thus very difficult to analyse, so that it is not really certain whether they contain any oxygen or not. They must contain the diazo group more or less unchanged because they can be reconverted into diazonium salts, if they have not exploded. The most interesting of the reactions of the diazotates, however, is their conversion into the isomeric isodiazotates, which was discovered by C. Schraube and C. Schmidt in 1894.[2] This isomeric change can be brought about by heating the solution of the diazotate with excess of alkali and takes place with different ease in different cases. The two isomers are not known in every case and only in a few has it been found possible to isolate the two solid isomeric salts in an analytically pure condition. Still, there are four or five cases known where this has been done and it has been shown that both have the same composition and molecular weight. The cause of this isomerism is discussed later. Both compounds behave as the salts of weak acids and are partially hydrolysed in solution, but the isodiazotates are considerably more stable than the normal diazotates, and in some cases are manufactured and sold for use in the preparation of azo dyes. Similarly the acids from which the isodiazotates derive, unlike the normal diazohydrates, can often be liberated from the salts by acids as somewhat unstable oils or solids. In solution they appear to undergo rearrangement into the primary nitrosamine, $Ar \cdot NH \cdot NO$ (see p. 422). All these compounds are closely related and all are reconverted to the diazonium salt by mineral acids. Their relations can be shown in the following scheme:

Mineral acid

Diazonium salt $\xrightarrow{\text{KOH}}$ n-diazotate $\xrightarrow[\text{with KOH}]{\text{heat}}$ isodiazotate $\xrightarrow[\text{acid}]{\text{acetic}}$ isodiazohydrate $\rightarrow$ nitrosamine.

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[1] A. Hantzsch and J. Lifschitz, *Ber.* 1912, **45**, 3011.   [2] Ibid. **27**, 514.

The second class of reactions, those in which the two nitrogen atoms of the diazo group are not lost as gaseous nitrogen, will now be described. There is one reaction which is common to all the possible forms of a diazo compound. This is reduction to a mono-substituted hydrazine,

$$Ar \cdot NH \cdot NH_2;$$

it is brought about by a large number of reducing agents and is discussed on p. 380. In the majority of the other reactions of this class there are marked differences between the diazonium salt and the diazotates, and minor differences between the normal diazotate and the isodiazotate. In one case it is a difference of kind and in the other of degree. The most important reaction is that usually known as the coupling reaction, a name which covers a large number of complicated processes. In general it may be said that the diazonium salts are unable to take part in the coupling reaction, except possibly with amines; that normal diazotates or diazo-hydrates couple extremely readily; and isodiazotates, isodiazohydrates and nitrosamines very much less rapidly and sometimes, perhaps, not at all. The coupling reaction takes place between a diazo compound and a compound which contains a hydrogen atom which may be linked to carbon, nitrogen, or oxygen; its essence is that the hydrogen atom is eliminated with the group attached to the diazo nitrogen atoms and that an azo compound is formed, in which the azo group takes the place of the hydrogen atom. Thus the coupling of sodium benzene diazotate with β-naphthol can be represented as follows:

Examples of this reaction which are of technical importance are coupling with phenols and aromatic amines, since, if the reaction takes place under the right conditions, the products are azo dye-stuffs; but in addition to these, diazo compounds can couple with a variety of other classes of substances, notably with phenolic ethers, with the enolic forms of β-diketones and β-ketonic esters, such as acetoacetic ester, and with reactive hydrocarbons, especially those which contain a system of conjugated double bonds, such as butadiene, $CH_2:CH \cdot CH:CH_2$, and cyclopentadiene.

The products formed in coupling with these various types of compounds are as follows:

With *primary and secondary aliphatic amines* coupling takes place with the nitrogen atom of the amino group and a diazoamino compound is formed.

$$Ar \cdot N_2X + RNH_2 \longrightarrow Ar \cdot N:N \cdot NH \cdot R$$

With primary amines the process can occur again and a bisdiazoamino compound may result (see p. 466).

With *primary and secondary aromatic amines* there is the same possibility of the formation of a diazoamino compound and this is often

obtained. A second possibility is direct coupling with the aromatic nucleus and the formation of a true azo compound; thus 2-methyl-4-amino-azo-benzene is obtained from diazobenzene and *m*-toluidine:

$$\phi \cdot N_2 \cdot OH + \underset{\text{CH}_3}{\bigcirc}\!\!-NH_2 \longrightarrow \phi \cdot N{:}N\!\!-\underset{\text{CH}_3}{\bigcirc}\!\!-NH_2.$$

With some amines, such as the naphthylamines, coupling with the nitrogen atom is never observed, and with others a C-azo or an N-azo compound is formed according to the hydrogen-ion concentration in the solution. When coupling with the carbon atom takes place, the azo group enters the position para or ortho to the amino group, and preferentially the former.

Tertiary aromatic amines couple readily. The product is a C-azo compound; a diazoamino compound cannot be formed, because there is no hydrogen atom in the amino group. Thus dimethylamino-azobenzene can be prepared from dimethylaniline:

$$Me_2N\!\!\bigcirc + HO \cdot N_2 \cdot \phi \longrightarrow Me_2N\!\!\bigcirc N{:}N \cdot \phi.$$

With *phenols* there are two similar possibilities, coupling to the oxygen atom or to a carbon atom of the ring; in the first case the product is a diazo-ether and in the second a hydroxy-azo compound. The latter is the usual product, and with the phenols themselves coupling preferentially takes place in the para position to the hydroxyl group of the phenol.

$$\phi \cdot N_2 \cdot OH + \bigcirc OH \longrightarrow \phi \cdot N{:}N\!\!\bigcirc OH$$

The phenolic ethers, such as anisole, only couple with the more reactive diazo compounds, such as those derived from the nitroanilines and the chloroanilines. The product is a C-azo compound.

With the *enolic forms of β-diketones and β-ketonic esters* the reaction is first with the hydroxyl group, but rearrangement of the O-azo into a C-azo compound takes place, followed by a further change into a hydrazone. Only in certain cases have all three stages been detected.[1]

$$\begin{array}{cccc} \text{R} \cdot \text{C} \cdot \text{OH} & \text{R} \cdot \text{C} \cdot \text{ON}_2\text{Ar} & \text{R} \cdot \text{CO} & \text{R} \cdot \text{CO} \\ \| & \longrightarrow \quad \| & \longrightarrow \quad | & \longrightarrow \quad | \\ \text{R}'\text{CO} \cdot \text{CH} & \text{R}'\text{CO} \cdot \text{CH} & \text{R}'\text{CO} \cdot \text{CH} \cdot \text{N}_2\text{Ar} & \text{R}'\text{CO} \cdot \text{C}{:}\text{N} \cdot \text{NHAr} \end{array}$$

This reaction usually proceeds further, by hydrolytic loss of one acyl group, to give the monophenylhydrazone of an α-dicarbonyl compound, $R' \cdot CO \cdot CH{:}N \cdot NH \cdot Ar$; it was first investigated by Japp and Klingemann in the case of ethyl methylacetoacetate which lost either the acetyl or the carbethoxy group according to the conditions.[2] The reaction may be used to detect the presence of an enolic group.

[1] O. Dimroth and M. Hartmann, *Ber.* 1908, **41**, 4012.
[2] See R. P. Linstead and A. B. Wang, *J.C.S.* 1937, 807.

With the *reactive unsaturated hydrocarbons* coupling takes place directly on to a carbon atom; thus 2,4-dinitrobenzene diazohydrate and isoprene give $CH_2:CH \cdot CMe:CH \cdot N:N \cdot C_6H_3(NO_2)_2$.[1]

Because of the commercial importance of the azo dyes (see p. 447) an enormous mass of empirical information has been obtained about the rates of coupling and the conditions and factors which affect the reaction. Nevertheless, the mechanism which leads to the formation of C-azo products, such as hydroxy- and amino-azo compounds, is not known with certainty. Since diazoamino compounds and diazo-ethers can be transformed by simple means into amino-azo and hydroxy-azo compounds, respectively, it was for long supposed that the first stage in coupling with a primary amine or phenol was the formation of the N- or O-azo compound which 'rearranged' to the C-azo product:

This view is untenable for two reasons: firstly, it offers no explanation for the C-coupling of tertiary amines and phenolic ethers in which intermediates of the diazoamino type cannot be formed, and secondly, it is now known that when a diazoamino compound 'rearranges' into an amino-azo compound the first stage is dissociation of the former under the action of the acid catalyst into a diazo compound and an amine, and the second stage is the direct coupling of these two to give the C-azo compound (see p. 459). Hence to consider the diazoamino compound as an intermediate in the C-coupling of an amine is a view which has no meaning whatever.

When K. H. Meyer discovered that coupling could take place with hydrocarbons which contain a conjugated system of double bonds, he thought that he had found the key to the problem and that the primary step in the coupling reaction is addition of the diazo compound to the unsaturated system. This first step could be followed by an elimination which would give the C-azo product. He formulated the coupling with anisole as:

A similar scheme can be constructed for an unsaturated hydrocarbon such as butadiene:

[1] K. H. Meyer, *Ber.* 1919, **52**, 1468.

A primary addition compound of the diazo compound and the other coupling component is undoubtedly formed. It has been observed in certain cases as a solid which separates from the solution and has a different crystalline form from either the diazoamino or amino-azo compounds;[1] it is, however, too unstable for satisfactory investigation and breaks down into various products according to the conditions. The evidence is insufficient to decide whether this primary addition complex has the structure allotted to it on Meyer's scheme. It is known that in the coupling of the methyl ethers of some phenols there is partial or complete loss of the methyl group during the reaction, so that the product contains a free phenolic hydroxyl group and not a methoxy group. This has been held to suggest that Meyer's scheme is inadequate, and that the oxygen atom of a phenol or the nitrogen atom of an amine is also involved in the formation of the complex and not only the unsaturated system.[2] The question must be left open until more information has been obtained. There is no direct evidence as to the structure of the complex, and it is, of course, possible that the structure may not be the same in all the types of coupling reactions which are known.

The Constitution of the Diazo Compounds

In the original structure which Griess proposed for the diazo compounds he regarded them as derived from the hydrocarbons by the replacement of two atoms of hydrogen by two of nitrogen, and supposed that they formed salts by addition of an acid, as is certainly the case with many organic bases. He postulated a compound diazobenzene, $C_6H_4N_2$, which formed a chloride, $C_6H_4N_2,HCl$. A. Kekulé had no difficulty in overthrowing such formulae, and in his *Lehrbuch* (1866) pointed out that in all the reactions in which the nitrogen atoms are lost a mono-substituted benzene remains. Hence the salt must be $\phi \cdot N_2Cl$, and this formula he expanded to $\phi \cdot N{=}N \cdot Cl$ and wrote the free base as $\phi \cdot N{=}N \cdot OH$. Soon after, another structure for the salt was proposed by W. Blomstrand in his text-book (1869). He considered that the salt was analogous to an ammonium salt and must contain pentad nitrogen. Hence he wrote the formula $\phi \cdot N{\underset{Cl}{\overset{N}{\diagup}}}$.

This same formula was supported by A. Strecker and P. Römer[3] on the ground that the unstable diazo compounds are so unlike the stable azo compounds, which are known to have the general formula $R \cdot N{=}N \cdot R$, that the two groups cannot have a similar structure, as Kekulé's formula suggests. E. Erlenmeyer independently suggested the same structure in

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[1] An excellent series of microphotographs showing the crystals of the complex from diazosulphanilic acid and *m*-phenylenediamine will be found in *Künstliche organische Farbstoffe*, Fierz-David, Berlin 1926, Tafel 5.

[2] P. Karrer, *Ber.* 1915, **48**, 1398, has reported that in the coupling of di-isoamyl and di-*n*-butylanilines one alkyl group attached to nitrogen is lost; this is disputed by J. Reilly and W. J. Hickinbottom, *J.C.S.* 1918, **113**, 99.

[3] *Ber.* 1871, **4**, 786.

1874[1] without giving much reason for it. Kekulé's formula was, however, generally accepted and interest focused rather on the practical use of the compounds than on their structure.

In 1892 the question of constitution was raised again by H. von Pechmann.[2] He had found that diazo toluene hydrate reacts with benzoyl chloride to give nitroso-toluanilide, $Me \cdot C_6H_4 \cdot N(NO) \cdot CO \cdot \phi$, and hence proposed the nitrosamine structure $Ar \cdot NH \cdot NO$. Two years later the problem entered on a new stage with the discovery of the isomeric diazotates which have been described above.[3] The first suggestion to account for the isomerism was that one salt derived from the diazohydrate $Ar \cdot N{=}N \cdot OH$, and the other from the nitrosamine $Ar \cdot NH \cdot NO$. In the same year Hantzsch published a paper[4] in which he reviewed the whole question and introduced an entirely new idea. He was fresh from his triumphant suggestion that the isomeric oximes were geometrical and not structural isomers, and he extended this proposal to the isomeric diazotates and isodiazotates. A prolonged controversy took place between Hantzsch and Bamberger which embraced the whole problem and was continued actively until about 1910. It cannot be followed in detail here, but it is of great interest in organic chemistry, because it led to a much clearer understanding and more precise formulation of the conceptions of tautomerism and stereoisomerism. Further, Hantzsch, for the first time in the history of organic chemistry, used physico-chemical measurements for elucidating the structure of organic molecules, and thus the experimental work he published during the controversy forms an important milestone in the development of organic chemistry. Hantzsch modified his views on several important points during the course of the controversy and eventually from the experimental material to which both parties had made valuable contributions he built up a theory of the structures of these compounds on as firm a basis as their properties and instability allow.

The main outlines of this theory received fairly general consent, including that of Bamberger,[5] until controversy broke out again in 1926, when the only other possible proposal that remained was vigorously supported by Angeli and his school in Florence. All the earlier ideas as to the diazotate-isodiazotate isomerism had assumed that the skeleton of the molecule was Ar—N—N—O and remained essentially the same in both compounds. Angeli's proposal was to throw over this idea and account for the isomerism by a difference in the position of the oxygen atom. Hantzsch in his old age (he died in his seventy-ninth year in 1935) took up the challenge and the controversy continued until 1931. It did not lead to any fundamental change in the views which had received general acceptance.

If we put aside for the moment Angeli's formula for the normal diazotate, the structures which have been proposed and for which supporting evi-

[1] *Ber.* **7**, 1116.   [2] Ibid. 1892, **25**, 3505.

[3] C. Schraube and C. Schmidt, ibid. 1894, **27**, 514; H. v. Pechmann and L. Frobenius, ibid. 672; E. Bamberger, ibid. 679.

[4] Ibid. 1702.   [5] Ibid. 1912, **45**, 2055.

dence could be found are shown below. Several other suggestions have been made, but on various grounds these are so improbable that they need not be discussed.

1. Kekulé's diazo formula, $Ar \cdot N = N \cdot OH$

2. Blomstrand's diazonium formula, $Ar \cdot N \diagdown^{N}_{OH}$

3. von Pechmann's nitrosamine formula, $Ar \cdot NH \cdot NO$

4. Hantzsch's stereoisomeric modification of Kekulé's formula

As will appear, all these formulae are correct under some conditions.

The salts of the diazo compounds with mineral acids offer less difficulty than the other derivatives. Here the evidence is overwhelmingly in favour of Blomstrand's view that pentad nitrogen must be present. The diazonium salts show the physico-chemical behaviour of the salts of a strong base, and resemble the salts of the alkali metals. Their carbonates are soluble in water with an alkaline reaction, and conductivity measurements show that they are completely ionized in dilute solution.[1] The diazonium salts contain a kation which is similar to that of a quaternary ammonium salt, and it must contain a nitrogen atom in a similar state of combination. Hence one of the nitrogen atoms must be tetra-covalent, and the only way in which this is possible is for the two nitrogen atoms to be united by a triple link. Consequently the formula of the kation is $[Ar \cdot \overset{+}{N} \equiv N]$. Since the four covalencies of pentavalent nitrogen have a space-arrangement which is similar to that of the four valencies of a carbon atom, the formula written in this way, with the two nitrogen atoms in a straight line with the carbon atom to which one is linked, is almost certainly an accurate representation of the arrangement of the constituent atoms of the kation in space.

When a quaternary ammonium salt is treated with a caustic alkali, the solution contains the free quaternary ammonium hydroxide, which behaves as a strong base. It has been mentioned already, however, that the diazonium hydroxides hardly exist, and that the action of excess of alkali on a diazonium salt converts it into a diazotate, that is, a salt which contains the diazo compound as anion. At first sight this behaviour is surprising, but it is by no means an isolated instance. Other quaternary hydroxides are known, especially those in which the nitrogen atom is doubly linked to carbon, which are unstable and tend to change into a non-basic substance, the nitrogen atom becoming trivalent; examples discussed in this book are the quaternary hydroxides derived from pyridine

[1] Hantzsch, ibid. 1895, **28**, 1737.

and quinoline (see p. 524). All quaternary ammonium salts in which the kation is capable of a suitable isomeric change, and the anion is that of a weak acid, show a more or less pronounced tendency to undergo the isomeric change, so that the anion becomes covalently linked and ceases to be an anion. The simplest example of the phenomenon is that of a weak acid itself, which, when liberated from its salt by a mineral acid, does not remain in the solution as kation and anion; the two ions unite to give the covalently linked undissociated acid. Thus the non-existence of the diazonium hydroxide is only an instance of a general phenomenon, and arises from the same causes as the non-existence of the diazonium cyanide, where the anion of the weak acid, prussic acid, is involved, and of the potassium diazonium sulphite; the two last cases are discussed later.

Hantzsch suggested that the change which takes place when a diazonium salt is treated with excess of alkali should be represented thus:

$$[Ar\overset{+}{-N}\equiv N]OH \longrightarrow Ar-N=N-OH.$$

In other words, he adopted Kekulé's formula for the diazohydrate. This view is perfectly satisfactory; the diazohydrate is a weak acid, indeed it is only stable in the form of its salts, and the formula contains the weakly acidic group :NOH, which is also found in the oximes. The diazotate, however, can be converted by simple means into an isomeric isodiazotate, as has been described above, and the long controversies about the constitution of the diazo compounds have been mainly concerned with the structures of these two isomers.[1] The alternatives are; (a) that the two compounds are geometrical isomers and can be represented by the formulae shown above, and (b) that they are structural isomers and contain different groups. There have been two different versions of the second alternative. The older view, originally suggested by Bamberger, was that one of the salts derives from the diazohydrate, which has a formula $Ar \cdot N{:}NOH$, and the other from the isomeric nitrosamine, $Ar \cdot NH \cdot NO$. The second version was Angeli's suggestion[2] that one comes from the diazohydrate, $Ar \cdot N{:}NOH$, and the other from the isomer, $Ar \cdot \underset{\downarrow}{N}{:}NH$. If it is
$$\overset{\downarrow}{O}$$
remembered that the compounds are hardly stable except as their salts with sodium or potassium, it will be realized that we are really discussing the structure of two anions, and that the isomerism implied by the two suggestions can be written:

$Ar-N=N-O^-$	$Ar-\overset{-}{N}-N=O$	$Ar-N\overset{\diagup O}{\diagdown N^-}$	$Ar-N=N-O^-.$
Diazotate	Isodiazotate	Diazotate	Isodiazotate
Bamberger		Angeli	

From this point of view Bamberger's formulae are very improbable, and

[1] An admirable discussion will be found in the article by J. Meisenheimer and W. Theilacker, *Stereochemie*, ed. K. Freudenberg, Leipzig, 1932, p. 1114.

[2] Summarizing paper, *Ber.* 1929, **62**, 1924.

in the end he abandoned them himself. The two isomers would only differ in distribution of electrons, and not in arrangement of their atoms, so that there would be nothing to hinder the instantaneous change of the less stable of the two into the more stable; two such formulae cannot represent isomeric compounds which retain their individuality in chemical reactions and physical properties.

Hantzsch's view that the isomerism is geometrical suffers from no such disadvantage and clearly has much to recommend it.

We know without any doubt that such isomerism exists in the unsymmetrical oximes and thus the arrangement of the nitrogen valencies in space must be such as to make it possible in the diazohydrates. Further, we know that geometrically isomeric oximes retain their difference as anions, so the analogy with the diazotate and isodiazotate is complete.

$$\begin{array}{cccc} \underset{R}{\diagdown}\underset{R'}{\diagup}C & \underset{R}{\diagdown}\underset{R'}{\diagup}C & \underset{Ar}{\diagdown}N & \underset{Ar}{\diagdown}N \\ \| & \| & \| & \| \\ N\diagdown O^- & {}^-O\diagup N & N\diagdown O^- & {}^-O\diagup N \end{array}$$

Almost all the arguments which have been urged against geometrical isomerism and in support of structural isomerism have been based on chemical reactions. Thus it was found that methylation of the sodium isodiazotate gives the N-methyl compound, $Ar \cdot NMe \cdot NO$, and this was quoted as support for the nitrosamine formula. Arguments of this kind, however, have proved notoriously unsound, as was rapidly shown in this case by the discovery that the silver salt gives the O-methyl ether, $Ar \cdot N : N \cdot OMe$. Angeli's view was largely based on the fact that benzene azoxy-carboxylic amide, of which the formula is known to be

$$\phi \cdot NO : N \cdot CONH_2,$$

can be hydrolysed to a product which couples with β-naphthol to give an azo dye. He assumed that the normal diazotate was formed in the hydrolysis which he wrote as $\phi \cdot NO : N \cdot CONH_2 \longrightarrow \phi \cdot NO : NK$, attributing the last formula to the normal diazotate. If, however, β-naphthol is not present during the hydrolysis, no normal diazotate can be detected; the main products are nitrobenzene and ammonia.[1] It therefore looks as though the azo dye came from some unstable intermediate which is not a diazotate. Further, it is possible to retort to such an argument with the fact that the normal diazotate is oxidized to a salt of a phenyl nitramine;[2] the structure of the latter compound is known to be $\left[\phi \cdot N : N \diagup_{O^-}^{O}\right] K$, so that this fact hardly supports Angeli's formula for the diazotate, $[\phi \cdot NO : N^-]K$. Another argument which has been urged against Hantzsch's view is that the absorption spectra of solutions of a diazotate and an isodiazotate differ

[1] A. Pieroni and G. Giannini, *Gazz.* 1924, **54**, 162; A. Hantzsch and E. Strasser, *Ber.* 1931, **64**, 655.   [2] E. Bamberger and O. Baudisch, ibid. 1909, **42**, 3568.

to a greater degree than with other types of geometrical isomers.[1] This argument is as inconclusive as the others; we have no sure grounds for predicting how close will be the resemblance between the absorption spectra of two geometrical isomers, and Meisenheimer[2] has found cases of isomeric oximes where the differences are just as great as with the diazotate and isodiazotate.

The strongest evidence in support of Hantzsch's view is derived from the study of the diazocyanides and diazosulphonates. If the isomerism is geometrical, it should not be confined to the diazohydrates, but might appear in other classes of compounds which have the diazo structure $Ar \cdot N = N \cdot X$. If, on the other hand, the structurally isomeric formulae are correct, a molecule in which X was not a hydroxyl group could not exist in two isomeric forms. When a solution of a diazonium salt is treated with potassium cyanide, momentarily the solution contains the diazonium and cyanide ions, but only in one case, where the diazonium hydroxide is an exceptionally strong base because of a methoxy group in the para position, can a diazonium cyanide, a salt-like compound, be isolated. In every other case there is the usual covalent attachment of the anion of a weak acid, and a diazocyanide results. This compound is not an electrolyte; it is soluble in organic solvents and is very reactive, losing nitrogen on the addition of copper powder, $Ar \cdot N_2 \cdot CN \longrightarrow Ar \cdot CN + N_2$, and coupling with phenols. The only structure it can be allotted is $Ar \cdot N : N \cdot CN$, which is analogous to that of a diazohydrate. On standing in the solid state or in alcoholic solution, it changes into an isomeric isodiazocyanide of similar physical properties and of the same composition and molecular weight; this compound is less reactive and only couples with difficulty. The isomerism cannot be that of a cyanide and an isocyanide, because neither shows the characteristic properties of an isocyanide and both can be converted into one and the same imino-ether,[3] $Ar \cdot N : N \cdot C(:NH)OEt$. Similarly treatment of a diazonium salt with potassium hydrogen sulphite gives the normal diazosulphonate (again the anion of a weak acid is involved), $Ar \cdot N : N \cdot SO_3K$, which shows no reactions of a sulphite, such as a precipitate with barium salts. This can be converted into an isomer which shows similar properties, but is less reactive; the isomer is often called Fischer's salt, and it was by the reduction of this salt that Emil Fischer first prepared phenylhydrazine (see p. 380). The sulphonates are less well known than the cyanides, but their properties and reactions indicate that they are related to one another just as are the cyanides. There is a possibility that in one a sulphur atom is united to nitrogen and in the other an oxygen atom, $Ar \cdot N : N \cdot SO_2 \cdot OK$ and $Ar \cdot N : N \cdot O \cdot SO \cdot OK$; the latter formula, however, represents the salt of a half-ester of sulphurous acid, and neither of the two isomers shows the properties of such a compound.

When we are faced in these three classes of compounds, the hydrates, the cyanides and the sulphonates, with the existence of two isomers which are

[1] L. Cambi and L. Szegö, *Ber.* 1928, **61**, 2081.   [2] Op. cit. p. 1118.

[3] A. Hantzsch and O. W. Schulze, *Ber.* 1895, **28**, 2073.

similarly related, it seems logical to assign the isomerism to a cause which is common to all the classes, and the only possible common cause is geometrical isomerism. This is the cogent reason for accepting Hantzsch's interpretation, and it is supported by the fact that for none of the special hypotheses which would account for the isomerism in each individual class can any satisfactory evidence be found.

Taking the existence of geometrical isomerism as proved for these compounds, the question remains whether it is possible to allot configurations to a pair of isomers. Can we say that in the normal diazotate the oxygen atom and aryl residue are on the same side of the doubly bound nitrogen atoms or not ? In all three series of compounds the isomers differ in that one is much more reactive than the other. Two geometrical isomers, both in the ethylenes and the oximes, differ in energy content and one is usually distinctly more stable than the other; the difference in energy arises necessarily from the fact that the distances between the constituent atoms of the molecule are different and thus the interactions between the atoms cannot be the same (see p. 202). Hantzsch made the assumption that the energy content of the *syn* form (I) is greater than that of the *anti* form (II), and hence allotted the *syn* structure to the normal diazotate.

$$\text{I.} \quad \begin{array}{c} \phi\diagdown \\ \quad \text{N} \\ \quad \| \\ \diagup\text{N} \\ {}^-\text{O} \end{array} \qquad \text{II.} \quad \begin{array}{c} \phi\diagdown \\ \quad \text{N} \\ \quad \| \\ \text{N} \\ \quad \diagdown\text{O}^- \end{array} \qquad \text{III.} \quad \begin{array}{c} \phi\diagdown \\ \quad \text{N} \\ \quad \| \\ \text{N} \\ \quad \diagdown\phi \end{array}$$

He based the assumption on the analogy with the majority of geometrically isomeric ethylenic compounds, such as maleic and fumaric acid, where the *trans* isomer is the more stable. The assumption that the more stable of the isomers has the *trans* configuration now finds further support in that of the two known forms of azobenzene the *trans* form (III) is more stable than the *cis* (pp. 437, 456); and again with the geometrically isomeric azoxy compounds (p. 431) the *cis* molecule is labile and passes over into the stable *trans* form. Without direct experimental evidence, however, Hantzsch's view remains a probable assumption and cannot be taken as firmly established. The relative stability of two such isomers depends on the nature of the groups in the molecule and it may be dangerous to argue by analogy with compounds which contain different groups. Even in the ethylenic compounds there are anomalies such as the fact that *cis*-dichloroethylene is more stable than the *trans* compound.[1]

Hantzsch advanced a number of other arguments in support of his views as to the configurations of the diazotates and isodiazotates, but further increase in knowledge about the behaviour of geometrical isomers has shown that none of these arguments can be held to carry any weight. His first argument was based on the fact that the normal diazotates and cyanides pass into a phenol or nitrile with loss of nitrogen more readily than the iso compounds. He assumed that if two groups lie on the same

[1] L. Ebert and R. Büll, *Z. phys. Chem.* 1931, A, **152**, 451.

side of a double bond, they are eliminated more readily from the molecule than if they are on opposite sides of that bond. Hence, he argued, the diazotates must be the *cis* isomers. He made the argument more striking by assuming further that the angles between the double bond uniting the nitrogen atoms and the single bonds linking the aryl and hydroxyl groups were each less than 90°, so that he represented the two isomers as in (IV) and (V), and said that it was clearly the *cis* compound which would lose nitrogen more easily.

IV.   V.

Hantzsch's assumption about the angles is extremely improbable, and is unsupported by any evidence. The three valencies of a trivalent nitrogen atom are arranged in space much as three of the valencies of a carbon atom, so that the angle between the single and double bonds is much more likely to be of the order of 125° rather than less than 90°. For this reason the purely steric interference implied by Hantzsch's formulae is unlikely, and the two isomers are more accurately represented by formulae such as (I) and (II). Apart, however, from this assumption about the angles, the first assumption that groups lying on the same side of a double bond will react together has been proved to be wrong in other cases, and so cannot be assumed without proper evidence here. The example which is most closely related to the diazotates is that of the oximes. A pair of isomeric aldoximes differ in that the acetyl derivative of one loses acetic acid under the action of alkali and is converted into a nitrile, while the acetyl derivative of the other is simply hydrolysed to the free oxime (see p. 183). The assumption was originally made that the groups eliminated as acetic acid lie on the same side of the double bond, but the evidence is now conclusive that this is not so, and that, in fact, in the acetyl oxime from which acetic acid can be split off the eliminated groups are on opposite sides of the double bond. Similarly in ethylenic geometrical isomers *trans* elimination usually takes place more readily than *cis*.

Hantzsch's second argument dealt with reactions involving ring closure which are shown by certain diazotates. P. Jacobson[1] found that a normal diazotate which contains a thiol (—SH) group in the ortho position is not converted into an isodiazotate by alkali, but loses the elements of water to form a cyclic diazosulphide :

[1] *Annalen*, 1893, **277**, 209.

Similarly, if there is a methyl group in the ortho position, no isodiazotate is formed, but water is eliminated and an indazole results.

Hantzsch consequently argued that in these normal diazotates the hydroxyl group must lie on the same side of the double bond as the aromatic residue. This assumption cannot be accepted without direct experimental evidence. The argument is incomplete because in these cases only one of the two possible isomers can be obtained and it is impossible to contrast the relative ease of ring closure of the two. More importantly, however, there are examples where similar assumptions are known to be false. The most striking of these is provided by the behaviour of the dioximes of benzil; the configurations of the β- and γ-dioximes are known beyond doubt, but it is only from the γ-dioxime that water can be eliminated to close the furazane ring.[1]

β-dioxime γ-dioxime

The position of our knowledge of the isomerism we have been discussing can be summarized in the following way. Where two isomeric compounds are known in the diazohydrates, -cyanides, and -sulphonates, the isomerism is geometrical. In all three classes the difference between the isomers is the same; one is distinctly more reactive and less stable than the other, and has the lower melting-point and, in consequence, the higher solubility. Hence it is almost certain that all the less stable forms have one and the same configuration, and all the more stable forms the other. Because of the instability of the compounds and the difficulty of working with them, there is no unambiguous evidence as to the configurations; hence it is premature to state definitely what the configurations are, but at the same time it is probable that the more reactive isomers are the *cis* compounds.

As has been stated above, the normal diazohydrates themselves are unknown; any attempt to liberate them from their alkali salts leads to decomposition to a phenol, formation of a 'diazoanhydride', or isomeric change into the isodiazohydrate. When a solution of an isodiazotate, however, is treated with acids at low temperatures, solid compounds are obtained, and their properties and behaviour have been studied by A. Hantzsch and W. Pohl.[2] The compounds are unstable and, in consequence, there is still a certain amount of doubt as to their true structure, although in the case of the *p*-nitrobenzene derivatives the facts are fairly well established. Addition of the equivalent of acetic acid to a cold solution of the isodiazohydrate precipitates a crystalline colourless solid, which

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[1] J. Meisenheimer and W. Lamparter, ibid. 1924, **57**, 276.   [2] *Ber.* 1902, **35**, 2964.

explodes on heating to 55°, but can be kept for some hours at ordinary temperature. The compound is converted into the diazonium chloride by passing hydrogen chloride into its solution in chloroform. If dissolved in cold benzene or chloroform it is transformed into an unstable yellow solid which does not give the diazonium chloride with hydrogen chloride in chloroform, nor can it be extracted from the chloroform solution by aqueous alkalis, although aqueous acids and alkalis give the diazonium salt and the diazotate, respectively. The same yellow solid is obtained by saturating the solution of the potassium isodiazotate with carbon dioxide. The observed behaviour of these compounds, unstable though they are, recalls that of an aliphatic nitro compound such as phenyl-nitromethane, especially in the precipitation of a non-acidic form by carbon dioxide and of an acidic form by a stronger acid (see p. 232). For this reason it seems likely that, as Hantzsch suggested, the two compounds are, respectively, the *aci*- and the neutral form of a pseudo-acid; the colourless solid is almost certainly the free isodiazohydrate, $O_2N \cdot C_6H_4 \cdot N:NOH$, and consequently the yellow less acidic form may well be the primary nitrosamine, $O_2N \cdot C_6H_4 \cdot NH \cdot NO$. The change from colourless to yellow form is accompanied by a profound change in the absorption spectrum[1] and there is some resemblance between the absorption of the neutral compound and of the compound $\phi \cdot N(CO \cdot CH_3) \cdot NO$, a fact which gives support to Hantzsch's views.

Another class of compounds derived from certain diazonium salts deserves a short description. These are the so-called diazo-phenols, which are formed by the action of alkali on diazonium salts in which there is a hydroxyl group in the ortho or para position to the diazo group. Their composition corresponds to the loss of water from the diazonium hydroxide, so that they are anhydro bases. They are distinctly more stable than most aromatic diazo derivatives. Their constitution gave rise to a certain amount of discussion, but there is now general agreement that they are quinone derivatives, as shown below, and contain two nitrogen atoms linked together as in the aliphatic diazo compounds (the linkage of these two nitrogen atoms is discussed in detail on p. 360).

The evidence for this view is that no similar compounds can be obtained in the meta-hydroxy series, and that the absorption spectra of the compounds resemble that of the aliphatic diazo compounds.[2] There is, however, another possible structure of the betaine type, in which the oxygen

[1] A. Hantzsch and J. Lifschitz, *Ber.* 1912, **45**, 3033.

[2] See, *inter alia*, G. T. Morgan and J. W. Porter, *J.C.S.* 1915, **107**, 645; Morgan and H. P. Tomlins, ibid. 1917, **111**, 497; A. Hantzsch and J. Lifschitz, *Ber.* 1914, **47**, 1407.

atom is negatively charged and the nitrogen atoms form a positively charged diazonium group.

These formulae differ from the others only in the position of electrons, and hence the actual structure may well be that of a resonance-hybrid of the two forms ; the resonance energy may account for the stability of the compounds. Mineral acids convert a diazo-phenol back into the diazonium salt by an addition reaction, as with other anhydro bases.

Among the many problems in the chemistry of the diazo compounds which still await complete solution is the nature of the solid diazonium salts. The majority of the sulphates and chlorides are colourless substances which behave as true salts, but the behaviour of the salts of other acids is sometimes remarkable. The extreme instability of the iodides has been mentioned already (p. 406), and this instability accompanied by the appearance of colour becomes very marked in the case of compounds which contain negative substituents such as chlorine or bromine in the benzene ring, and also among the halides as the atomic weight of the halogen increases. Thus 2,4,6-tribromobenzene diazonium chloride is colourless, fairly stable, and soluble in water, but the bromide is golden yellow, only sparingly soluble in water, and explosive when dry. Hantzsch has suggested that in the solid salts there is a tautomerism between the diazonium and diazo structure, $[\text{Ar} \cdot \overset{+}{\text{N}} {\equiv} \text{N}]\text{Br} \rightleftharpoons \text{Ar} \cdot \text{N}{=}\text{N} \cdot \text{Br}$, and because tautomeric equilibrium in the solid state is only possible if the tautomers form a solid solution, he assumed that such solid solutions are formed. There is insufficient experimental evidence to prove or disprove such a view, but a more likely explanation seems to lie in the phenomena of ionic deformation which Fajans has investigated. In the case of the salts of the alkali metals Fajans finds anomalies in the refractivities of the more concentrated solutions which become more marked as one proceeds from the chloride to the iodide. Fajans attributes these effects to the mutual deformations of the ions, so that with a large monatomic anion the linkage between kation and anion becomes almost a covalency.[1] It may well be that something similar is happening in the diazonium salts. According to Fajans's results the sulphate ion is one of the least deformable and, in agreement with this, the diazonium sulphates seem uniformly to show normal properties.

The last question that remains for discussion is why diazo compounds of the type discussed in this chapter only exist if the diazo group is attached to an aromatic nucleus. In addition to the benzene derivatives, which are the best known, diazo compounds of similar structure and

[1] K. Fajans, Ž. *Elektrochem.* 1928, **34**, 502.

properties are known in certain heterocyclic systems such as pyrazole, thioazole, and pyrrole, but nothing comparable is known among the aliphatic compounds. There is no doubt that the reason for their existence has something to do with the conjugation of the unsaturation of the diazo group with the unsaturation of the aromatic system, although it is not easy to be more precise. How intimately the whole of the aromatic structure is bound up with the diazo group can be illustrated in two ways. Firstly, there is the marked effect of the nature of the substituents attached to the benzene ring on the stabilities of the substituted benzene diazonium salts; and this effect is found not only with the substituent in the ortho position where it is close to the diazo group, but also in the para position, so that it must be transmitted through the conjugated system.

Many examples of this effect could be quoted: an interesting one is that a positively charged group, $-\overset{+}{N}Me_3$, shows the same stabilizing effect as a nitro group, just as they both have the same orientating effect in benzene substitution, and that with the quaternary ammonium derivatives, the diazonium compounds become less stable the further the stabilizing positive charge is removed from the conjugated system. In the following series[1] the compounds are shown in order of decreasing stability:

$$N\equiv\overset{+}{N}-\!\!\left\langle\ \right\rangle\!\!-\overset{+}{N}Me_3 \ > \ N\equiv\overset{+}{N}-\!\!\left\langle\ \right\rangle\!\!-CH_2\cdot\overset{+}{N}Me_3$$

$$> \ N\equiv\overset{+}{N}-\!\!\left\langle\ \right\rangle\!\!-CH_2\cdot CH_2\cdot\overset{+}{N}Me_3$$

The second illustration is the effect of the diazonium group on the substituents attached to the aromatic ring. In certain diazonium salts a remarkable exchange reaction takes place between the anion and a halogen substituent in the ortho or para position to the diazo group. The effect was first found by Hantzsch and B. Hirsch[2] in the case of p-chlorobenzenediazonium thiocyanate. This unstable and somewhat explosive salt gives solutions which show the characteristic reactions of the thiocyanate ion. If to its alcoholic solution a few drops of strong hydrochloric acid are added, and then ether, a solid salt can be obtained which shows no thiocyanate reactions in aqueous solution and is identical with p-thiocyanobenzenediazonium chloride.

$$Cl-\!\!\left\langle\ \right\rangle\!\!-\overset{+}{N}\equiv N[SCN] \ \longrightarrow \ NCS-\!\!\left\langle\ \right\rangle\!\!-\overset{+}{N}\equiv N[Cl]$$

Similarly 2,4-dibromobenzene diazonium chloride becomes chlorobromobenzenediazonium bromide, and other cases are known. Considering how unreactive a chlorine or bromine atom attached to an aromatic nucleus is in most respects, this result is a striking indication of the interrelation between the diazonium group and the aromatic structure. It recalls the

[1] J. Reilly and P. J. Drumm, *J.C.S.* 1935, 871.　　　[2] *Ber.* 1896, **29**, 947.

curious mobility which is shown by para halogen substituents in the triphenylmethyl free radical.

The following list gives some examples of amines derived from heterocyclic aromatic systems from which true diazonium salts have been obtained. It should be noticed that only β-amino pyridines and quinolines, as distinct from the α- and γ-compounds, can be diazotized under ordinary conditions to give typical diazonium salts (see p. 529).

4-Amino-pyrazoles, such as

$$\begin{array}{c} NH-CMe \\ | \qquad \diagdown C\cdot NH_2 \\ N=\!\!\!=CMe \end{array}$$

4-Amino-pyrazolones, such as

$$\begin{array}{c} MeN-CMe \\ | \qquad \diagdown C\cdot NH_2 \\ \phi\cdot N-CO \end{array}$$

2-Amino-thiazoles, such as

$$\begin{array}{c} CH-S \\ \| \qquad \diagdown C\cdot NH_2 \\ CH-N \end{array}$$

5-Amino-1,2,4-triazoles, such as

$$\begin{array}{c} N-\!\!\!-NH \\ \| \qquad \diagdown C\cdot NH_2 \\ CH-N \end{array}$$

β-Amino-quinolines, such as

AZOXY AND AZO COMPOUNDS AND OTHER COMPOUNDS CONTAINING TWO LINKED NITROGEN ATOMS

THE AZOXY COMPOUNDS[1]

THE azoxy compounds form a small class of stable substances which are produced, often very readily, in the reduction of an aromatic nitro compound in alkaline solution (see p. 252). Azoxybenzene, the best-known member of the class, was first prepared by N. Zinin in 1841 by the action of alcoholic potash on nitrobenzene.[2] The compounds are of little or no practical importance, but their structure and isomerism present several points of interest. Azoxybenzene has the formula $\phi \cdot N_2O \cdot \phi$: it is readily reduced by heating with iron filings to azobenzene, $\phi \cdot N:N \cdot \phi$; hence in the azoxy compound each nitrogen is linked directly to a phenyl group and not by means of an oxygen atom. The compounds are not basic and are not attacked by oxidizing agents. On these simple grounds Kekulé suggested that the oxygen atom was attached to both nitrogen atoms and wrote the formula of the characteristic azoxy group —N_2O— as

$$-N\underset{O}{\overset{\textstyle \diagdown\diagup}{\rule{0pt}{0pt}}}N-.$$

This structure was generally accepted for many years, until A. Angeli, in investigations during the years 1910–20, proved that the group was not symmetrical by preparing isomers of the formulae

$$X—N_2O—Y \quad \text{and} \quad Y—N_2O—X.$$

The lack of symmetry in the group can only mean that the oxygen atom is attached to one nitrogen atom and not to both, and hence Angeli proposed the formula $—\overset{\parallel}{\underset{O}{N}}=N—$, in which one nitrogen atom is shown as pentaco-

valent. Since no compounds are known which contain nitrogen with an outer shell of ten valency electrons, it is clear that the link uniting nitrogen to oxygen is a co-ordinate (semi-polar) link, as, for example, in the N-ethers of oximes (p. 173), and the azoxy group must be represented by the formula $—\overset{\downarrow}{\underset{O}{N}}=N—$. In the majority of the azoxy compounds known the two groups attached to the nitrogen atoms are aromatic radicals.

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[1] Monographs on this subject are: H. E. Bigelow, *Chem. Rev.* 1931, **9**, 117; A. Angeli, *Ahrens' Sammlung*, 1913, **19**, 447; 'Die Azoxyverbindungen', E. Müller, *Ahrens' Sammlung*, Neue Folge 33, Stuttgart, 1936.

[2] *J. pr. Chem.* 1841, **36**, 93.

The commonest method for the preparation of azoxy compounds is the reduction of a nitro compound. As has been discussed above (p. 253) the azoxy compound results from the condensation of the nitroso compound and the hydroxylamine produced during the reduction,

$$R \cdot NO + HONH \cdot R \longrightarrow R \cdot NO:N \cdot R + H_2O$$

and for the azoxy compound to be formed the conditions must be such that this condensation can take place. A variety of reducing agents have been used, the most usual being sodium methoxide in methyl alcohol, or sodium arsenite. Only symmetrical azoxy compounds can be obtained by this method; for example, azoxybenzene, $\phi \cdot NO:N \cdot \phi$, in which both carbon radicals are identical.

The nitroso compound and the hydroxylamine can be prepared separately and condensed together to give a good yield of the azoxy compound;[1] the condensation takes place most readily in the presence of alkali (see p. 254). If the nitroso compound and the hydroxylamine contain different groups, e.g. p-bromo-phenylhydroxylamine and nitrosobenzene, the product would be expected to consist of the unsymmetrical azoxy compound, $Br \cdot C_6H_4 \cdot N_2O \cdot \phi$. In one or two cases this actually occurs, for example, p-nitrosophenol and phenylhydroxylamine give p-hydroxy-azoxybenzene, $\phi \cdot N_2O \cdot C_6H_4OH$.[2] With these few exceptions, however, this does not take place and, strangely enough, a mixture of the two symmetrical azoxy compounds is formed, e.g. $\phi \cdot NO:N \cdot \phi$ and $Br \cdot C_6H_4 \cdot NO:N \cdot C_6H_4 \cdot Br$. This fact has never been explained satisfactorily, but the same kind of phenomenon has been observed in other reactions. Because of this condensation between a nitroso compound and a hydroxylamine and because azoxy compounds are stable, they are formed in a variety of decompositions of nitroso compounds and aromatic hydroxylamines. Any reaction in which a nitroso compound is reduced or an aromatic hydroxylamine is oxidized will give a certain amount of an azoxy compound, if the reaction mixture is not so strongly acid that the condensation is inhibited.

The only other method for preparing azoxy compounds is the oxidation of an azo compound,

$$Ar \cdot N:N \cdot Ar \longrightarrow Ar \cdot NO:N \cdot Ar,$$

and for this a powerful oxidizing agent is needed. The best is hydrogen peroxide (30 per cent.) dissolved in glacial acetic acid. This is the reagent which Angeli first used and which enabled him to carry out his important work on the structure of these compounds, for, apart from reactions such as the bromination of azoxybenzene itself, it is the only general method known whereby the unsymmetrical azoxy compounds can be obtained. The reaction is carried out at room temperature or on the water-bath and sometimes takes several days, but in many cases it gives a quantitative yield. The glacial acetic acid is essential to the reaction because the actual oxidizing agent is the unstable peracetic acid formed by the interaction of the hydrogen peroxide and acetic acid.

[1] E. Bamberger and E. Renauld, *Ber.* 1897, **30**, 2278.

[2] E. Bamberger, ibid. 1900, **33**, 1941, 1953.

The ordinary azoxybenzene (there is a geometrically isomeric form which is discussed below) is a faintly yellow solid melting at 36°. It is insoluble in water and unattacked by alkalis and dilute acids. Nearly all azoxy compounds crystallize extremely well and some of them behave as anisotropic liquids (liquid crystals) over a range of temperature immediately above their melting-points, the best known being p-azoxyanisole, MeO—⟨◯⟩—NO:N—⟨◯⟩—OMe, and the corresponding ethyl ether. Their reduction to azo compounds by mild agents has been mentioned already: vigorous reducing agents, such as stannous chloride, reduce them rapidly to two molecules of a primary amine:

$$Ar \cdot NO:N \cdot Ar \longrightarrow ArNH_2 + H_2NAr.$$

Towards strong hydrochloric acid they are completely stable, but if warmed with concentrated sulphuric acid, they undergo a curious rearrangement which is often called, after its discoverer, the Wallach transformation.[1] The products of this rearrangement are hydroxy-azo compounds, and with azoxybenzene the main product is the para derivative:

⟨◯⟩—NO:N—⟨◯⟩ ⟶ HO⟨◯⟩—N:N—⟨◯⟩

A certain amount of the ortho-hydroxy compound is also formed if the heating is carried out on the water-bath, and this amount is much increased if the mixture is heated to 220°. The same rearrangement also takes place if an alcoholic solution of azoxybenzene is exposed to the light of a mercury-vapour lamp,[2] but in this case the product is the ortho compound. Nothing is known of the mechanism of this rearrangement.

Azoxybenzene is readily nitrated and brominated, the substituent entering the para position to the azoxy group, but only one of the two phenyl groups is attacked. The position where substitution has taken place is, of course, easily determined by identifying the amines formed on reduction. The fact that only one of the two aromatic nuclei is attacked is itself an indication that the true formula of the azoxy compounds is not a symmetrical one and that the two aromatic nuclei are not linked to two similar nitrogen atoms.[3]

The true structure of the azoxy compounds was revealed by Angeli's discovery of cases of isomeric compounds. When a symmetrical azo compound such as azobenzene is oxidized with peracetic acid, the product is a single compound, but if an unsymmetrical azo compound is used, in most cases a mixture of two compounds is obtained. Thus p-nitroazobenzene, $O_2N \cdot C_6H_4 \cdot N:N \cdot \phi$, gives an azoxy compound, melting-point 152°, which is identical with the substance formed in the nitration of azoxybenzene, and an isomer melting at 149°. Similarly, two p-bromoazoxybenzenes, melting-points 73° and 92°, are obtained from p-bromoazo-

[1] O. Wallach and L. Belli, *Ber.* 1880, **13**, 525.
[2] W. M. Cumming and G. S. Ferrier, *J.C.S.* 1925, **127**, 2374.
[3] Mrs. G. M. Robinson, ibid. 1917, **111**, 111.

benzene. Neither isomer can be transformed into the other by light, heating, dilute acids, or alkalis, which would appear to exclude geometrical isomerism, but both can be reduced to the same azo compound. Consequently the isomerism appears to be due to the structure of the azoxy group. The isomers differ very markedly in their behaviour in substitution reactions. Both in the case of the p-nitro and of the p-bromo compound, one isomer is easily brominated or nitrated while under the same conditions the other is not attacked. From this fact Angeli was able to deduce the actual structures of the two isomers. If p-bromoazobenzene,

$$Br \cdot C_6H_4 \cdot N : N \cdot \phi,$$

is treated with bromine or nitric acid, substitution takes place very readily with the formation of p,p'-dibromoazobenzene or p-bromo-p'-nitroazobenzene, a fact which indicates that the trivalent nitrogen atom of an azo group directs the substituent to the para position and, as in most cases of ortho-para orientation, substitution takes place readily. If now we must deduce from the existence of these isomers that the oxygen atom is attached to only one of the two nitrogen atoms in the azoxy group, the structures of the two p-bromoazoxybenzenes will be (I) and (II), and a difference in their substitution reactions is to be expected. One of the

nitrogen atoms is trivalent and in very much the same state as a nitrogen atom in an azo group, but the other is 'pentavalent' (tetracovalent) like the nitrogen atom of a nitro group and must be meta-directing. Now with a meta-directing substituent attached to a benzene ring, substitution takes place very much less readily than with an ortho-para-directing substituent. Hence in (I) where the ring with the free para position is attached to the pentavalent nitrogen atom substitution should be much more difficult than in (II). The isomers differ precisely in this fashion and this is not only evidence that Angeli's structure of the azoxy group is correct, but it also indicates the structures which must be assigned to the two isomers.

The nomenclature of the isomers is somewhat confusing; the convention originally adopted was that the compound which was obtained most easily or was prepared first was called the α-compound and the other the β-compound. Actually both with p-nitro and p-bromoazoxybenzenes the α-compound does not undergo further substitution while the β- does, and thus structure (I) represents α-p-bromoazoxybenzene and (II) the β-compound. Hence the prefixes α and β are used to distinguish between the two structures, irrespective of which compound was the first to be obtained, and α implies that the substituent is attached to the benzene ring which is linked to the trivalent nitrogen atom.

There are two pieces of evidence which confirm Angeli's views. The

first is the fact that bromination of β-p-nitroazoxybenzene and nitration of β-p-bromazoxybenzene do not give the same product:[1] this can be shown thus:

$$\langle\ \rangle-N:NO-\langle\ \rangle NO_2 \qquad\qquad \langle\ \rangle-N:NO-\langle\ \rangle Br$$
$$\text{m.p. }148° \qquad\qquad\qquad \text{m.p. }92°$$
$$\downarrow \qquad\qquad\qquad\qquad\qquad \downarrow$$
$$Br\langle\ \rangle-N:NO-\langle\ \rangle NO_2 \qquad O_2N\langle\ \rangle-N:NO-\langle\ \rangle Br$$
$$\text{m.p. }203° \qquad\qquad\qquad \text{m.p. }194°$$

The second is especially valuable because it is of a different nature.[2] α-p-Azophenylbutyric acid (III)[3] contains two asymmetric carbon atoms, marked with asterisks, which are identical. Hence there must be a dl acid

$$\text{III. } HO_2C\cdot\overset{*}{C}HEt\langle\ \rangle-N:N-\langle\ \rangle-\overset{*}{C}HEt\cdot CO_2H$$

which can be resolved, and a non-resolvable meso acid. Two acids were obtained and one could be resolved. This azo compound can be oxidized to an azoxy compound. If the azoxy group is symmetrical, the two asymmetric carbon atoms are still identical and there should still be a dl acid and a meso acid; if the azoxy group is unsymmetrical, the asymmetric carbon atoms are no longer identical and, as with any compound with two dissimilar centres of asymmetry, there must be two distinct dl acids, both of which are resolvable, so that two distinct dextro forms and two distinct laevo forms should exist. All these four optically active acids were actually obtained, and there can be no doubt as to the essential truth of Angeli's structure.

If we now consider the arrangement in space of the component parts of a molecule of a symmetrical azoxy compound such as azoxybenzene, it will be seen that, though structural isomerism is impossible because the two phenyl groups are alike, geometrical isomerism might occur. Both an oxime (IV) and its N-phenyl ether (V) exist in geometrically isomeric forms, and the two nitrogen atoms of an azoxy compound (VI) resemble those in these two compounds, respectively.

$$\text{IV.} \quad \overset{R\diagdown\ \diagup R'}{\underset{\overset{N}{\diagdown OH}}{\overset{\|}{C}}} \quad \overset{R\diagdown\ \diagup R'}{\underset{\overset{N}{HO\diagup}}{\overset{\|}{C}}} \qquad\qquad \text{V.} \quad \overset{R\diagdown\ \diagup R'}{\underset{\overset{N}{O\swarrow\ \phi}}{\overset{\|}{C}}} \quad \overset{R\diagdown\ \diagup R'}{\underset{\overset{N}{\phi\diagup\ \searrow O}}{\overset{\|}{C}}}$$

[1] A. Angeli and B. Valori, *Atti R.* 1912 [v], **21**, i. 155.

[2] T. T. Chu and C. S. Marvel, *J. Amer. C. S.* 1933, **55**, 2841.

[3] α here indicates the position of substitution in the butyric acid chain: this is one of the few legitimate uses of the Greek letters in organic nomenclature: for all other uses alternative prefixes are to be preferred.

VI. *a.*   *b.*

$$\phi\diagdown \nearrow O \qquad \phi\diagdown \nearrow O$$

The plane formulae shown in (VI) must be accurate representations of the molecule; the four valencies of tetracovalent nitrogen are similar to those of carbon in their spatial distribution, and hence, since the oximes (IV) are known to have a planar structure, the azoxy compounds (VI) will have the same.[1] The geometrical isomers predicted by these formulae have been obtained. A. Reissert[2] found that when nitrosobenzene was reduced with aqueous alcoholic potash at room temperature two products were obtained, the ordinary azoxy compound, melting-point 36°, and an isomer which he called iso-azoxybenzene, melting-point 84°. Since then several other pairs of isomers have been obtained,[3] and all of them contain two identical groups attached to the azoxy residue so that they cannot be position-isomers of Angeli's type. Their behaviour is entirely different from the true position-isomers: one compound is unstable and, by the action of heat or of light, is very readily transformed into the other. The absorption spectra of the two isomers are not identical, which shows that the compounds retain their difference in solution and are not polymorphs, but are of the same general type as is true for the majority of geometrically isomeric substances.[4] The electric moments of several pairs of isomeric molecules have been measured,[5] and in each case the moment of the unstable iso-compound is greater than that of the stable form: e.g. azoxybenzene, $\mu = 1\cdot7\,D$; iso-azoxybenzene, $\mu = 4\cdot7\,D$. It is impossible to calculate from measurements on other compounds what will be the moments of the models (VI *a* and *b*), because of the unknown interaction between the various links. But since we know that in the link C—N the carbon is positive to the nitrogen and in N→O the nitrogen is positive to the oxygen, it is clear that the unstable iso forms have the *cis* configuration (VI *b*) and the ordinary compounds the *trans* configuration (VI *a*), as might have been expected. The difference in moment is, however, surprisingly large.

THE AZO COMPOUNDS

The azo compounds contain two hydrocarbon radicals attached to the azo group —N=N— and have the general formula R—N=N—R'. If the radicals R and R' are the same the compound is usually called by a name in which azo is prefixed to the name of the compound from which the radicals are derived: thus $CH_3\cdot N:N\cdot CH_3$ is azomethane, $\phi\cdot N:N\cdot\phi$ azo-

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[1] No reasons have been adduced by K. A. Gehrckens and E. Müller (*Annalen*, 1933, **500**, 296) for their assumption that the azoxy molecule is not planar.

[2] *Ber.* 1909, **42**, 1364.   [3] E. Müller, *Annalen*, 1932, **495**, 132.

[4] Ibid. 1932, **493**, 166.

[5] Gehrckens and Müller, loc. cit.

benzene, and $EtO_2C \cdot CMe_2 \cdot N:N \cdot CMe_2 \cdot CO_2Et$ azo-isobutyric ethyl ester. If the radicals are different, the word azo is placed between the names of the two compounds, as in benzene-azo-methane, $\phi \cdot N:N \cdot CH_3$. This system suffices for the simpler compounds but soon breaks down for the complicated members of the class which are used as dye-stuffs. Indeed, many of these are so complicated that systematic names for them are completely impracticable and trivial names alone are used.

The azo compounds differ profoundly from the diazo compounds, such as the diazohydrates or cyanides which also contain doubly linked nitrogen atoms, in that they are stable and, on the whole, non-reactive substances. The azo compounds can be divided into the following classes which will be discussed separately.

(i) Aliphatic azo compounds in which both radicals are aliphatic.

(ii) Mixed azo compounds in which one radical is aliphatic and the other aromatic.

(iii) Aromatic azo compounds in which both radicals are aromatic.

(iv) Hydroxy-azo compounds, aromatic azo compounds containing a hydroxyl substituent.

(v) Amino-azo compounds, aromatic azo compounds containing an amino substituent.

The last two classes, which raise special problems, include the vast array of azo dye-stuffs.

Of the aliphatic azo compounds, azomethane is the best known. It is prepared by oxidizing an aqueous solution of *symm*-dimethylhydrazine hydrochloride with potassium bichromate, and since it is a gas at room temperature and is soluble in water, it is distilled from the reaction mixture under reduced pressure:

$$CH_3 \cdot NH \cdot NH \cdot CH_3 \longrightarrow CH_3 \cdot N:N \cdot CH_3.$$

It can be condensed to a yellow liquid which boils at $1 \cdot 5°/751$ mm. Its aqueous solution is neutral and it shows no sign of basic character. It is reduced by zinc dust in aqueous alkali to dimethylhydrazine and is decomposed by strong hydrochloric acid to formaldehyde and monomethylhydrazine. This latter reaction is apparently the hydrolysis of the tautomeric hydrazone.

$$CH_3 \cdot N:N \cdot CH_3 \longrightarrow CH_3 \cdot NH \cdot N:CH_2 \longrightarrow CH_3 \cdot NH \cdot NH_2 + CH_2O$$

There is, however, no other indication of tautomeric change into the hydrazone, although many other azo compounds change readily and irreversibly into hydrazones (see below). Unlike the aromatic azo compounds, azomethane decomposes on heating to temperatures above 200°, and the products consist almost entirely of nitrogen and ethane together with a little methane and ethylene:

$$CH_3 \cdot N:N \cdot CH_3 \longrightarrow CH_3 \cdot CH_3 + N_2.$$

The decomposition can take place as a homogeneous unimolecular reaction,[1]

[1] H. C. Ramsperger, *J. Amer. C. S.* 1927, **49**, 912, 1495; B. Lewis, *Proc. Nat. Acad. Sci.* 1927, **13**, 546.

and seems to be a simple disruption into a molecule of nitrogen and two free methyl radicals. The latter can be detected in the decomposing gas by the usual method of their effect on thin mirrors of metals such as lead, which they attack with the formation of the metallic alkyl compound.[1]

The majority of aliphatic azo compounds, including those which contain carbethoxy groups such as azoisobutyric ester,

$$EtO_2C \cdot CMe_2 \cdot N : N \cdot CMe_2 \cdot CO_2Et,$$

behave very much like azomethane; they lose nitrogen on heating and hardly show any unsaturated properties apart from reduction. On the other hand, azoformic ester, $EtO_2C \cdot N : N \cdot CO_2Et$, which is usually called azodicarboxylic ester, behaves quite differently and possesses the most extraordinary powers of adding on to other unsaturated systems. It is an orange-coloured oil prepared by the oxidation of hydrazine dicarboxylic ester (from hydrazine and chloroformic ester) with strong nitric acid; it is much more stable to heat than the majority of aliphatic azo compounds. With compounds that contain an open system of conjugated double bonds addition takes place at room temperature in the absence of any catalyst and a large variety of products can be obtained. The addition usually takes place in the 1:4-positions of the conjugated system and is an example of the so-called Diels-Alder reaction. Thus with cyclopentadiene the product is (I) and with butadiene (II).[2] The ester can even react with

I.   II.

an aromatic hydrocarbon if a little hydrogen chloride and a trace of iodine are present: naphthalene combines with two molecules of the ester to give (III).[3] In some cases it will add on to a conjugated system which is part

III.   IV.

of an aromatic structure: styrene when mixed with the ester gives in the cold the compound (IV) by addition to form a bicyclic system followed by

[1] J. A. Leermakers, *J. Amer. C. S.* 1933, **55**, 3499; F. O. Rice and B. L. Evering, ibid. 3898.   [2] O. Diels, J. H. Blom, and W. Koll, *Annalen*, 1925, **443**, 242.
[3] R. Stollé and G. Adam, *J. pr. Chem.* 1926, **111**, 167.

further addition to that system.[1] It also forms addition compounds of various types with enols and amines. It can be used to remove a methyl group attached to nitrogen in a secondary amine; the ester and amine unite to give a crystalline compound, which breaks up when boiled with dilute acids into formaldehyde and the primary amine.[2]

$$R \cdot NH \cdot CH_3 \longrightarrow \begin{array}{c} RNH \cdot CH_2 \cdot N \cdot CO_2Et \\ | \\ NH \cdot CO_2Et \end{array} \longrightarrow RNH_2 + CH_2O + \begin{array}{c} NH \cdot CO_2Et \\ | \\ NH \cdot CO_2Et \end{array}$$

Azodicarboxylic ester is converted into the diamide by concentrated aqueous ammonia and this can be hydrolysed by cold potash to the potassium salt of the acid. The salt decomposes in aqueous solution at room temperature:

$$2 KO_2C \cdot N{:}N \cdot CO_2K \longrightarrow 2K_2CO_3 + N_2H_4 + N_2 + 2CO_2.$$

The chief interest of the mixed azo compounds lies in their isomeric change into hydrazones, a complicated question which cannot be discussed here in detail.[3] The hydrocarbon derivatives such as benzene-azo-ethane, $\phi \cdot N{:}N \cdot C_2H_5$, can be prepared by the oxidation of the corresponding hydrazine, $\phi \cdot NH \cdot NH \cdot C_2H_5$, best by shaking the ethereal solution with yellow mercuric oxide.[4] Benzene-azo-ethane is a pale yellow liquid which boils at about 180° with slight decomposition. It does not lose nitrogen so readily as azomethane; the presence of one aromatic nucleus brings about the beginnings of the temperature-stability so marked in azobenzene. If it is treated with acids or alkalis it undergoes isomeric change into the phenylhydrazone of acetaldehyde, a colourless crystalline substance whose remarkable isomerism has been mentioned on p. 397.

$$\phi \cdot N{:}N \cdot CH_2 \cdot CH_3 \longrightarrow \phi \cdot NH \cdot N{:}CH \cdot CH_3$$

If it is heated with aqueous acids, phenylhydrazine and acetaldehyde are formed, the hydrolysis products of the hydrazone. There is no evidence that an equilibrium is set up between azo compound and hydrazone in this case, although benzene-azo-methane is formed in small yield by the action of formaldehyde on phenylhydrazine, which suggests that the change may be reversible.

$$\phi \cdot NH \cdot N{:}CH_2 \longrightarrow \phi \cdot N{:}N \cdot CH_3$$

Benzene-azo-ethane is typical of such mixed azo compounds: they can often be obtained, but they tend to pass with more or less ease into hydrazones by the change in position of a hydrogen atom.

When other groups are present in the molecule, there is the same tendency to go over to the hydrazone structure, but the phenomena which have been observed are surprising. Diazo compounds of the aromatic series will couple with various types of aliphatic compounds, and since the

[1] O. Diels and K. Alder, *Annalen*, 1927, **450**, 237.

[2] O. Diels and Ernst Fischer, *Ber.* 1914, **47**, 2043.

[3] For the older work see H. Wieland, *Die Hydrazine*, Stuttgart, 1913, p. 130 et seq.

[4] Emil Fischer, *Ber.* 1896, **29**, 794.

coupling products with aromatic amines and phenols were known to be azo compounds, it was thought at one time that in the aliphatic cases the products were mixed azo compounds. Thus acetoacetic ester and similar keto-enol tautomers couple easily with diazo compounds to give products which were thought to have the structure

$$CH_3 \cdot CO \cdot CH(CO_2Et) \cdot N : N \cdot Ar.$$

After a long controversy (see Wieland's monograph for references) it became clear that the compounds do not have this structure, but are really hydrazones, such as $CH_3 \cdot CO \cdot C(CO_2Et) : N \cdot NH \cdot Ar$. When there is no hydrogen atom on the carbon atom attached to nitrogen, this kind of simple isomeric change is impossible and the azo structure might be expected to show greater stability. Compounds with the azo group attached to a tertiary carbon atom exist, but even with them isomeric change to the hydrazone takes place, although it involves the migration of an acyl or alkyl group. If benzene diazonium chloride is coupled with tribenzoylmethane, a mixed azo compound can be obtained as red crystals melting at 168°. This substance changes into a colourless isomer (melting-point 203°) by heating in the solid state to 120°, or more readily in solution: the isomer is the N-benzoylphenylhydrazone of diphenyl triketone (V), as is shown by the fact that with alkalis it gives the phenylhydrazone and on reduction benzanilide ($\phi \cdot CO \cdot NH\phi$).[1]

$$(\phi \cdot CO)_3CH \longrightarrow (\phi \cdot CO)_3C \cdot N : N \cdot \phi \longrightarrow (\phi \cdot CO)_2C : N \cdot N\phi \cdot CO\phi$$
$$V.$$

Often the true azo compound cannot be isolated; an acyl group is lost and a hydrazone formed. Thus methylacetoacetic ester is converted into the phenylhydrazone of pyruvic ester (VI). If the ester of the β-keto-acid is replaced by the sodium salt, the carboxyl group is lost and the acyl group remains.[2]

$$CH_3 \cdot CO \cdot CHMe \cdot CO_2Et \longrightarrow \phi NH \cdot N : CMe \cdot CO_2Et \quad (VI)$$

Even an alkyl group migrates sometimes. If p-bromobenzene diazonium chloride is added to a weakly alkaline solution of ethylcyanoacetic ethyl ester, a crystalline product can be obtained which is the bromophenylethyl hydrazone (VII). This is shown both by its reduction to ethylaniline and by its identity with the compound obtained by the ethylation of the hydrazone $Br \cdot C_6H_4 \cdot NH \cdot N : C(CN) \cdot CO_2Et$.[3]

$$Et \cdot CH(CN) \cdot CO_2Et \longrightarrow Br \cdot C_6H_4 \cdot NEt \cdot N : C(CN) \cdot CO_2Et$$
$$VII.$$

The true reason for these surprising rearrangements is not known and their mechanism has not been explored.

The aromatic azo compounds show many reactions which are similar to those of the aliphatic and mixed compounds, but differ from them in their great stability to heat. Azobenzene, $\phi \cdot N : N \cdot \phi$, which forms bright

[1] O. Dimroth and M. Hartmann, ibid. 1908, **41**, 4012.

[2] R. H. F. Manske, W. H. Perkin, and R. Robinson, *J.C.S.* 1927, 2.

[3] G. Favrel, *Bull. Soc. chim.* 1930, [iv], **47**, 1290.

orange-red crystals melting at 66°, boils without decomposition at 295°. The typical aliphatic decomposition with loss of nitrogen does not take place smoothly even at high temperatures, for even in a red-hot tube aniline, prussic acid, and ammonia are formed.

When nitrobenzene is reduced in alkaline solution a small amount of azobenzene is formed by side reactions which have been discussed (p. 254). It is best prepared from azoxybenzene by gentle reduction, but because of the ease with which it can be reduced further to hydrazobenzene, $\phi NH \cdot NH \phi$, the reducing agent should be of the type which removes oxygen from the molecule, but cannot add on hydrogen. The usual procedure is to distil azoxybenzene slowly with dry iron filings. Another useful method for preparing aromatic azo compounds in general is by the oxidation of the corresponding hydrazo compound.

$$Ar \cdot NH \cdot NH \cdot Ar \longrightarrow Ar \cdot N : N \cdot Ar$$

This is similar to the preparation of the aliphatic members of the group, but it takes place with much greater ease. In the presence of alkali atmospheric oxygen will oxidize hydrazobenzene to azobenzene, hydrogen peroxide being formed at the same time as in several similar cases. In the laboratory almost any gentle oxidizing agent can be used. Hydrazobenzene decomposes above its melting-point by a process of mutual oxidation and reduction into azobenzene and aniline:

$$2\phi \cdot NH \cdot NH \cdot \phi \longrightarrow \phi \cdot N : N \cdot \phi + 2\phi NH_2.$$

Taking the normal values for the heats of formation of singly and doubly bound nitrogen atoms, the reaction is exothermic, evolving 15 kg. cals. for each gram-molecule. The same process will take place at room temperature in the presence of finely divided palladium which seems to act as a carrier of hydrogen from one molecule to the other.[1] Other reactions are known in which azo compounds are formed and are useful for preparing those which contain two different aromatic radicals. If an amine and a nitro compound are heated to 200° with powdered caustic soda, a mixture of an azoxy and an azo compound is formed: the reaction probably first gives the azoxy compound which is reduced at the high temperature to the azo compound.

$$Ar \cdot NH_2 + O_2N \cdot Ar' \longrightarrow Ar \cdot N : NO \cdot Ar' \longrightarrow Ar \cdot N : N \cdot Ar'$$

Another method which is a clear indication of the structure of the compounds is the condensation of an amine with a nitroso compound.[2]

$$Ar \cdot NO + H_2N \cdot Ar \longrightarrow Ar \cdot N : N \cdot Ar$$

If the two compounds contain different aromatic residues, a good yield of the unsymmetrical azo compound is formed: thus p-toluidine and nitrosobenzene or aniline and p-nitrosotoluene give an almost theoretical yield of benzene-azo-p-toluene.[3] This fact stands in curious contrast with the difficulty of obtaining unsymmetrical azoxy compounds from a nitroso compound and a hydroxylamine (see p. 427).

[1] H. Wieland, *Ber.* 1912, **45**, 484.

[2] E. Bamberger, ibid. 1893, **26**, 473.   [3] C. Mills, *J.C.S.* 1895, **67**, 925.

Of the reactions of the aromatic azo compounds their oxidation by peracetic acid to azoxy compounds has been mentioned above (p. 427). They are easily reduced, first to a hydrazo compound and then, the molecule being split between the nitrogen atoms, to two primary amine molecules. Stannous chloride or titanous chloride in acid solution are most commonly used for this purpose; the reaction is of importance for discovering the structure of dye-stuffs containing the azo group, the amines formed by reduction being separated and identified. The azo compounds are unaffected by aqueous acids and alkalis and show hardly any true basic properties. They are soluble in concentrated hydrochloric and hydrofluoric acids and compounds can be obtained from these solutions which contain the acid. Whether these are true salts or not, it is difficult to say. The absorption spectra of azobenzene in hydrochloric acid and in an organic solvent show very considerable differences.[1]

Azo compounds contain doubly linked nitrogen atoms, and hence the question of their configuration in space arises. From our knowledge of the stereochemistry of the oximes and the diazo-hydrates and -cyanides (pp. 175 and 417) it is clear that there are two possible arrangements, which can be described as *trans* and *cis*:

trans　　　　　　　　　　*cis*

Until 1937 no azo compound was known to occur in two geometrically isomeric forms: all the cases where two isomers were thought to exist had been found to be in error.[2]

The actual configuration of azobenzene cannot, of course, be deduced from any of its reactions, but the two structures must show differences in physical properties, because the *trans* molecule has a centre of symmetry and the *cis* molecule has not. That ordinary azobenzene has the *trans* configuration is shown by the fact that its molecule has no electric moment,[3] and is confirmed by investigation of its crystal structure.[4] The arrangement of the phenyl groups in the crystal is very similar to that in stilbene, $\phi CH:CH\phi$, which is known to be a *trans* compound. Azomethane, $MeN:NMe$, has also been shown to be a *trans* compound by means of the electron diffraction of the vapour.[5]

A note on the discovery and properties of *cis*-azobenzene is given at the end of the chapter (p. 456).

[1] A. Hantzsch, *Ber.* 1909, **42**, 2131.
[2] See, e. g., H. B. Hartley and J. M. Stuart, *J.C.S.* 1914, **105**, 309.
[3] E. Bergmann, L. Engel, and S. Sándor, *Ber.* 1930, **63**, 2572.
[4] J. M. Robertson, M. Prasad, and I. Woodward, *Proc. Roy. Soc.* 1936; A, **154**, 187.
[5] H. Boersch, *Sitz. Akad. Wiss. Wien*, 1935, ii *b*, **144**, 17; *Monats.* 1935, **65**, 327.

The Hydroxy-azo Compounds

This group of compounds together with the amino-azo compounds includes all the substances which are used as azo dyes and forms the largest of all known groups of organic compounds. None occur in nature; they have almost all been synthesized by coupling aromatic diazo compounds with phenols and aromatic amines. Any diazo compound can be coupled with almost any phenol or amine, sometimes in more than one way and sometimes more than once, and the product, if it contains an amino group that can be diazotized, can be used for further coupling reactions, so that molecules of the greatest complexity, containing any number of azo groups, can be made; it would be rash to give an estimate of the total number of compounds which have been prepared.

A brief account of these two groups of compounds considered as dyestuffs is given later. In addition to their importance in this respect, the properties of both groups raise problems which are of much greater theoretical interest, so that the simpler compounds will be discussed first.

The hydroxy-azo compounds are the hydroxy derivatives of the aromatic azo compounds. They can be formed in a variety of reactions, of which the Wallach transformation of an azoxy compound has already been described. The most commonly used method is to couple a diazo compound and a phenol; the mechanism of the reaction has been discussed above (p. 412). The reaction takes place best in weakly alkaline solution unlike the coupling with an amine where weakly acid solution is needed. Meta-hydroxy-azo compounds cannot, of course, be obtained by this method, because the azo group always enters the para or ortho position with respect to the hydroxyl group. It is impossible to summarize the known facts about the orientation of the products of the coupling reaction in a few sentences. In general one can say that if the para position is free, the azo group will enter there and that if it is filled, the azo group will sometimes displace the substituent, especially if it is carboxyl. Thus hydroxyisophthalic acid gives a monocarboxylic acid:

In the naphthalene series α-naphthol gives the p-azo compound (I) and β-naphthol invariably the α-azo compound (II), but in the amino naphthols and their sulphonic acids, which are the important azo dye intermediates,

the coupling is often in the ortho position, even where the para position

is free. In some exceptional cases the position taken up by the entering azo group depends on the nature of the diazo compound as well as on that of the phenol.

The simplest member of this class of compounds, *p*-hydroxyazobenzene, was prepared by Kekulé in 1870; it forms orange crystals and was generally accepted as a true azo-phenol, as is suggested by its colour and the fact that like a phenol it is soluble in dilute alkali. It can also be prepared by the condensation of aniline and nitrosophenol, a reaction which is similar to one of the methods for preparing azobenzene (p. 436), and this was held to support the same formula.

$$HO-\langle\ \rangle-NO + H_2N \cdot \phi \longrightarrow HO-\langle\ \rangle-N:N \cdot \phi$$

In 1883, however, T. Zincke obtained by the action of phenylhydrazine on α-naphthaquinone the same compound as was formed by coupling diazobenzene with α-naphthol. The latter method suggests an azo-structure, but the former could be interpreted to mean that the compound is a hydrazone.

$$O=\langle\ \rangle=O + H_2N \cdot NH\phi \longrightarrow O=\langle\ \rangle=N \cdot NH \cdot \phi$$

$$HO-\langle\ \rangle + HO \cdot N_2\phi \longrightarrow HO-\langle\ \rangle-N:N \cdot \phi$$

Hence arose the question of the true structure of these compounds, a question which has been the cause of a controversy which has continued almost without a break from Zincke's discovery onwards.[1] General agreement has been reached on a certain number of points, but there are others which remain obscure. The question became more acute when the contrast between the properties of the isomeric ortho and para naphthol compounds were known. Of the three compounds, 4-benzene-azo-α-naphthol (I) and 1-benzene-azo-β-naphthol (III) are readily obtained by coupling

I.   II a.   II b.

[1] An excellent historical account is in *Die Hydrazine*, H. Wieland, Stuttgart, 1913, p. 154 et seq.

$$N:N\cdot\phi$$

—OH

III a.

$$N\cdot NH\cdot\phi$$

=O

III b.

with α- and β-naphthol, respectively: 2-benzene-azo-α-naphthol (II) is formed in small amount in the coupling reaction of α-naphthol, but is best prepared by Zincke's method of condensing phenylhydrazine with β-naphthaquinone. The first compound is alkali-soluble and in most respects a phenol, and hence an azo compound. The two latter are insoluble in aqueous alkali, are indifferent to even so vigorous a methylating agent as diazomethane, and do not react at all readily with phenyl isocyanate, which seems to indicate the absence of a hydroxyl group. They will form sodium salts with sodium ethoxide in ethyl alcohol, but these are immediately decomposed by water so that they are very much weaker acids than the para compounds. The simplest conclusion to draw from these facts is that the para compounds have the azo structure, and that the ortho compounds are hydrazones (II b and III b), and this view is still held by some. It will be impossible to follow the twisting mazes of the controversy. The distinction between the ortho and para series is common to the whole group of compounds, and there seems no doubt that the para compounds are in fact phenols and azo compounds. This point is most clearly shown by the properties of meta-hydroxy-azobenzene. The compound cannot be prepared by any direct method; if, however, o-methoxyaniline is coupled with diazobenzene, the azo group enters the para position to the amino group. From the product, by elimination of the amino group (p. 405) and demethylation by heating with dry aluminium chloride (methyl chloride escapes and leaves the aluminium salt of the phenol), m-hydroxy-azobenzene can be obtained.[1]

The importance of this compound is that, since meta-quinones cannot be formed, it can be treated as a reference substance for a true azo-phenol structure. It resembles the para derivative closely. Both compounds are alkali-soluble and act as true acids by forming ammonium salts with ammonia in dry toluene; and both are somewhat associated in solution like most hydroxylic substances, while the ortho compound differs in these particulars.

The problem thus resolves itself into the question of the structure of the

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[1] P. Jacobson and F. Hönigberger, *Ber.* 1903, **36**, 4102.

ortho series of compounds. Although to assign to them a quinone-hydrazone structure has the advantage of simplicity, it has certain disadvantages. In general, especially in the benzene series, ortho-quinones are more difficult to obtain and less stable than para-quinones, yet here the para compound is not a quinone, while to the stable ortho compounds an ortho-quinone structure is allotted. If the hydrogen atom whose position is under debate is replaced by an acyl group such as benzoyl, $\phi \cdot CO$—, the stability relationships support this view of the improbability of a quinone structure. The behaviour of these benzoyl derivatives gave rise to much confusion[1] because the ease with which the benzoyl group migrates was not realized. Eventually it was proved[2] that, although in the para series N-benzoyl compounds can be obtained by condensing benzoylphenyl-hydrazine, $\phi \cdot CO \cdot N\phi \cdot NH_2$, with a para-quinone, the benzoyl group migrates very readily to the oxygen atom to give the isomeric O-benzoyl compound which cannot, of course, be a quinone.

$$O = \langle \bigcirc \rangle = N \cdot N\phi \cdot CO\phi \longrightarrow \phi \cdot CO \cdot O - \langle \bigcirc \rangle - N : N \cdot \phi$$

In the ortho series the N-benzoyl derivative cannot be obtained; migration to oxygen takes place and the only product is the O-benzoyl compound. Again, although ortho and para series differ in many ways, there are some important resemblances. A typical phenolic property is the ease with which substitution takes place with bromine and nitric acid, and in this respect both ortho and para compounds behave as phenols.[3]

The conclusions which have been drawn from the physical properties of the compounds are equally at variance. Measurements of the light-absorption are said to show beyond doubt that the ortho series are quinone-hydrazones,[4] while the molecular refractivities support the view that they are azo-phenols.[5] In view of all this conflict of evidence it would appear that the assumption made in all these arguments, that it is a question of quinone-hydrazone azo-phenol tautomerism, is in error and that something more complicated is lying behind the apparently irreconcilable facts. This remark does not imply that the tautomerism is impossible; indeed, many reactions in both the ortho and para series find their readiest explanation in the view that all these compounds can react at times as though they had either structure. If arguments from chemical reactions alone are admitted, much evidence could be produced in support of the view that the para compounds, in spite of their resemblance to the meta series, have the quinone structure. It has, for example, been shown[6] that a condensation of a Diels-Alder type takes place between a p-hydroxy-azo compound

[1] See Wieland, op. cit.

[2] K. v. Auwers and M. Eckhardt, *Annalen*, 1908, **359**, 336.

[3] J. T. Hewitt, *J.C.S.* 1900, **77**, 99, 712; 1901, **79**, 155, 160.

[4] A. Burawoy, *Annalen*, 1934, **509**, 60; see also R. Kuhn and F. Bär, ibid. 1935, **516**, 143.

[5] K. v. Auwers and E. Wolter, ibid. 1931, **487**, 79.

[6] W. M. Lauer, and S. E. Miller, *J. Amer. C. S.* 1935, **57**, 520.

and cyclopentadiene, and such a reaction is typical of a quinone and not shown by a benzenoid compound.

$$\phi\cdot N\!:\!N\!-\!\!\!\bigcirc\!\!\!-OH \longrightarrow \phi\cdot NH\cdot N\!=\!\!\!\bigcirc\!\!\!=\!O$$

$$\longrightarrow \phi\cdot NH\cdot N\!=\!\!\!\bigcirc\!\!\!=\!O$$

CH—CH$_2$—CH

CH=CH

There are two possibilities beyond simple tautomerism which have been suggested. Both are proposals about the structure of the ortho compounds, because it is really only with these that there is any serious trouble. It seems hardly likely that they are quinones and yet they refuse to behave as phenols. The first suggestion was made by P. Pfeiffer[1] and by F. A. Mason,[2] who pointed out that in the ortho compounds there is the possibility of the formation of a chelate ring, while such hydrogen-bond formation is impossible in the para series. Such a state can be considered as derived either from the benzenoid form (IV) or the quinonoid form (V). These formulae are only alternative ways of expressing the same thing

IV.   V.

(see the Introduction). There are two facts which indicate that this chelation is actually present. The first is that the ortho compounds do not show the absorption in the infra-red characteristic of either the —OH or the —NH— group.[3] The second is that the ortho compounds form stable complexes with certain metals,[4] which are typical chelated compounds, insoluble in water and soluble in chloroform and benzene; one atom of the metal unites with two or three molecules of the azo compound according to its valency and replaces the hydrogen atom shown in formulae (IV) and (V). If the compound can form chelate metallic complexes, it is highly probable, to judge from similar cases, that it itself forms a hydrogen-

[1] *J. pr. Chem.* 1930, **126**, 108.

[2] *J. Soc. Dyers and Colour.* 1932, **48**, 293.

[3] S. B. Hendricks, O. R. Wulf, G. E. Hilbert, and V. Liddel, *J. Amer. C. S.* 1936, **58**, 1995.

[4] See N. V. Sidgwick, *Electronic Theory of Valency*, 234 et seq.; M. Elkins and L. Hunter, *J.C.S.* 1935, 1598, where a full list of references will be found.

bond. The insolubility in alkali of the ortho compounds cannot, however, be adduced as evidence of chelation, since compounds such as o-nitrophenol are acidic although chelated (see p. 268). If the chelate ring actually exists in the ortho compounds, it can only do so in virtue of resonance between the forms (IV) and (V), and the compounds cannot be said to possess either of these individual structures.

But there are still further possibilities in the formulation of these compounds and the evidence for them is best shown in the behaviour of α-Naphthol Orange (VI), a sulphonic acid derived from one of the simple compounds which has been discussed.[1]

HO—⟨naphthyl⟩—N=N—⟨phenyl⟩—SO$_3$H   HO—⟨naphthyl⟩—N=N$^+$R—⟨phenyl⟩SO$_3^-$

VI.   VII.

This compound is soluble in alkalis, being not only a phenol but also a sulphonic acid, and for the latter reason it is somewhat soluble in water. It behaves as an indicator and its yellow solutions become red when alkali is added; the hydrogen-ion concentration at which it is half in the red form and half in the orange form (the turning-point) is about 10^{-8}. In spite of the fact that an acid such as benzene sulphonic acid is a strong acid which is completely dissociated in dilute solution, Naphthol Orange shows no conductivity whatever, and hence must be present as an internal salt or zwitterion (VII, R = H). This is not surprising from the point of view of the sulphonic group, but the azo nitrogen atoms in azobenzene are at the most very weakly basic, and so the fact that they are sufficiently basic to enter into salt formation in this compound is unexpected. This internal salt formation has, however, nothing to do with the indicator properties. These latter must mean a change of structure when the compound forms its sodium salt, i.e. gives up a proton and becomes an anion. It cannot be the proton that has left the sulphonic group and attached itself to one of the azo nitrogen atoms for the following reason. With dimethyl sulphate the compound gives a yellow monomethyl derivative in which the position of the methyl group is established by the facts that it is not removed by hydriodic acid, and thus cannot be attached to the phenolic oxygen or the sulphonic group, and that on reduction p-amino-α-naphthol is formed and this contains no methyl group. Hence the structure of the monomethyl derivative must be something like (VII, R = Me). But it is still an indicator with the same turning-point as the unmethylated compound, and must be capable of the same structural change on salt formation. If Naphthol Orange or its monomethyl derivative is treated with diazomethane in the absence of alkali, a dimethyl compound can be obtained. This substance is no longer an indicator; it must have the structure (VIII) because the

[1] K. H. Slotta and W. Franke, Ber. 1931, 64, 86.

methyl groups are not removed by hydrolysis with hydriodic acid and reduction gives p-methylamino-α-naphthol. This immediately shows that

$$^-O-\!\!\!\bigcirc\!\!\!\bigcirc\!\!\!-\overset{+}{N}Me\!\!=\!\!\overset{+}{N}Me-\!\!\!\bigcirc\!\!\!-\overset{-}{S}O_3$$

VIII.

the true structure of the original compound in acid solution is a double zwitterion (IX) which forms a salt with alkali by losing a proton from the nitrogen atom attached to the naphthalene ring and thus gives an anion capable of structural change into the red quinone (X).

$$^-O-\!\!\!\bigcirc\!\!\!\bigcirc\!\!\!-\overset{+}{N}H\!\!=\!\!\overset{+}{N}H-\!\!\!\bigcirc\!\!\!SO_3^- \rightleftharpoons O\!\!=\!\!\bigcirc\!\!\!\bigcirc\!\!\!=\!\!N\!\!-\!\!NH-\!\!\!\bigcirc\!\!\!-SO_3^-$$

IX. Yellow in acid solution   X. Red in alkaline solution

In view of the results of this brilliant investigation, it is not surprising that R. Kuhn[1] pointed out that the zwitterion constitution of this hydroxy-azo compound might be extended to other cases. He proposed a zwitterion structure for the ortho series of hydroxy-azo compounds in general, a possibility which hitherto had been overlooked (XI). This formula was extremely ingenious because it combines the azo-phenol and quinone-hydrazone

$$N\!\!=\!\!\overset{+}{N}H\cdot\phi$$
$$\bigcirc\!\!\!\bigcirc\!\!\!O^-$$

XI.

formulae: the position of the atoms is the same as that in the hydrazone but the arrangement of the valencies is the same as in the azo compound. The complete answer to the question of the constitution of these compounds cannot, of course, be given, but it seems that all the formulae, (IV) (V) and (XI), are to some extent correct. They differ simply in electron distribution and not in the position of the constituent atoms, and almost certainly there must be resonance between them. From this point of view the main reason for the marked differences between the compounds of the ortho and para series is because there are not the same possibilities of resonating states in the latter. Further, the actual structure of the molecule of an o-hydroxy-azo compound cannot, on this view, be represented by any one formula, and it is not surprising that attempts to correlate its physical properties with one particular formula have led to such confusing and contradictory results.

[1] *Naturwiss.* 1932, **20**, 622.

The Amino-azo Compounds

The amino-azo compounds are the amino derivatives of the aromatic azo compounds. As with the hydroxy-azo compounds, those with the amino group in the para and ortho position to the azo group are the easiest to prepare and the best known. They can be obtained by a variety of methods of which the following are the more important:

(i) They are formed in the 'rearrangement' of a diazoamino compound in the presence of acids:

$$\phi\cdot NH\cdot N:N\cdot\phi \longrightarrow \phi\cdot N:N\cdot C_6H_4\cdot NH_2.$$

The usual product is the p-amino compound, but ortho-amino derivatives are sometimes obtained if the para position is blocked. The mechanism of this reaction is discussed in detail later (p. 459).

(ii) They can be obtained by the condensation of a nitroso compound with a diamine, if one of the amino groups of the latter has been protected by acylation. The acyl group is removed later by hydrolysis. This is the only good method for preparing the meta compounds.

$$\phi\cdot CO\cdot NH-\!\!\bigcirc\!\!-NH_2 \quad \xrightarrow{\ \phi\cdot NO\ } \quad \phi\cdot CO\cdot NH-\!\!\bigcirc\!\!-N:N\cdot\phi$$

$$\longrightarrow \quad H_2N-\!\!\bigcirc\!\!-N:N\cdot\phi$$

(iii) They are formed in the coupling reaction between diazo compounds and aromatic amines, the mechanism of which has been discussed above (p. 412). The coupling takes place best in neutral or weakly acid solution and is inhibited both by excess of acid and of alkali. With a simple primary amine the product is usually a diazoamino compound, but with all tertiary amines, the majority of secondary amines, and some primary amines (notably m-phenylene diamine and the naphthylamines) the first product that can be obtained is an azo compound. The azo group enters preferentially the para position to the amino group, but if this is occupied, ortho coupling can take place in certain cases. In the naphthalene series, where the compounds are of technical importance, the behaviour is more complex and the presence of substituents has a great effect on the position taken up.[1] In the case of an amino-phenol or naphthol, the amino group acts as the directing group if coupling takes place in acid solution, but the hydroxyl acts as the directing group in alkaline solution.

The simpler amino-azo compounds are yellow or brown crystalline substances and their chemical properties present few points of interest. The amino group can be acylated and diazotized, and the compounds are reduced by vigorous agents to a mixture of a monoamine and a diamine:

$$\phi\cdot N:N\cdot C_6H_4\cdot NH_2 \longrightarrow \phi\cdot NH_2 + H_2N\cdot C_6H_4\cdot NH_2.$$

[1] See J. C. Cain and J. F. Thorpe, *Synthetic Dyestuffs*, London 1933, p. 92.

There are differences in the ortho and para series of compounds; the ortho compounds are oxidized to the azimido compounds to which the structure (XII) has been allotted. But these differences arise from the proximity of

XII.

the amino and azo groups in the ortho compounds and there is not the great difference between the two series that is observed in the hydroxy-azo compounds. This fact supports the view that in the latter something more than benzenoid-quinonoid tautomerism is involved.

The chief point of difficulty which these compounds present is the colour of the salts they form with mineral acids. The hydrochloride of p-amino-azobenzene as commonly prepared forms deep violet crystals, and similar salts are formed by many other compounds of the class. If amino-azo-benzene is treated with hydrogen chloride in ethereal solution, a hydro-chloride of much paler colour is precipitated; different descriptions of the colour have been given: J. Thiele, who first obtained it, describes it as pale pink or flesh-coloured,[1] but others call it yellow or leather-coloured. The pale salt is less stable than the violet salt and is rapidly transformed into it by traces of acid, by heating, and also, rather surprisingly, by rubbing the crystals with a spatula. Both salts seem to have the same molecular weight in phenol,[2] and analysis shows they are both mono-hydrochlorides. Other compounds of this class are known which give two salts of different depth of colour and in most cases the more deeply coloured salt is the more stable. On the other hand, certain of the com-pounds give only one salt which is of pale colour, and the more interesting examples are the ammonium compound $\phi \cdot N:N \cdot C_6H_4 \cdot NMe_3[Cl]$, which is orange, and the corresponding iodide, which is pink; also the salts of o-amino-azobenzene which are greenish yellow and give green solutions. In general the colours of the solutions of all these salts do not seem to have been recorded very accurately, but it appears[3] that the violet salts give violet solutions, while some of the pale salts are violet in chloroform but yellow in acetone.

Since marked change in colour usually implies a change in structure, A. Hantzsch[4] advanced the theory that the pale and dark coloured salts of p-amino-azobenzene have fundamentally different structures, that of the yellow salt being a normal azo compound (XIII) and the violet the quinone derivative (XIV).

XIII.   XIV.

[1] *Ber.* 1903, **36**, 3965.   [2] A. Hantzsch, ibid. 1909, **42**, 2129.
[3] Ibid. 1908, **41**, 1184.   [4] Ibid. 1908, **41**, 1184; 1909, **42**, 2129.

Since the ammonium salts mentioned above are pale in colour and presumably cannot change into the quinone structure, he assigned formula (XIII) to the pale hydrochloride and (XIV) to the ordinary violet salt. There is no direct evidence of the truth of this theory and it clearly raises many difficulties.[1] Measurements of light absorption show[2] that while azobenzene and azobenzene-trimethylammonium iodide,

$$\phi \cdot N : N \cdot C_6H_4 \cdot NMe_3[I],$$

have a similar absorption, that of dimethylamino-azobenzene,

$$\phi \cdot N : N \cdot C_6H_4 \cdot NMe_2,$$

and azobenzene are widely different, even with the latter as a free base and not as a salt. The absorption bands of the violet hydrochloride of the dimethylamino compound are, on the other hand, very similar to those of the yellow free base from which it derives, though shifted towards the red. These facts cannot be reconciled with Hantzsch's simple theory, because dimethylamino-azobenzene contains no hydrogen atom which can migrate to give a quinone structure, and undoubtedly has the true azo structure. In spite of this, its absorption resembles that of the violet salt in type. Another difficulty is that one compound of structure similar to (XIV) is known: it is quinone-anil diphenylhydrazone,[3] $\phi_2 \cdot N \cdot N : C_6H_4 : N \cdot \phi$: it is a monacid base and gives violet salts, but its absorption spectrum is of quite a different type from that of the violet salts of the p-amino-azobenzenes. The existence of difficulties of this kind make it unnecessary to discuss Hantzsch's simple theory any further. Nevertheless, the problem of the different absorption spectra of these compounds and their salts remains to be solved.[4]

The Azo Dye-stuffs[5]

In view of the importance of the hydroxy-azo and to a less extent the amino-azo compounds as dyes, it may be useful to give some brief account of the main types of azo dyes and of how they are used. Dye-stuffs are, of course, coloured compounds which can be caused to adhere to or combine with a fibre such as cotton, wool, silk, and the artificial silks or a material such as leather. The colour of a dye comes from the light-absorption of one or more groups in the molecule. Such a group is called a chromophore and in the dyes under discussion the chromophore is the azo group —N=N—. The absorption is very much affected by the presence of other groups, and those which increase the absorption and

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[1] See H. Wieland, op. cit. p. 171 et seq.

[2] A. Hantzsch, *Ber.* 1909, **42**, 2133.

[3] H. Wieland, ibid. 1910, **43**, 3260.

[4] See also D. Vorländer and E. Wolferts, ibid. 1923, **56**, 1229; A. Hantzsch and A. Burawoy, ibid. 1930, **63**, 1760.

[5] For a fuller account consult books such as *The Synthetic Dyestuffs*, J. C. Cain and J. F. Thorpe, London, 1933: *Künstliche organische Farbstoffe*, H. E. Fierz-David, Berlin, 1926; *Ergänzungsband*, 1935.

deepen the colour, such as —OH, —NH$_2$, were called by O. N. Witt auxo-chromes. The power of combining with various fabrics is also determined by the presence of certain groups in the molecule. Many of the groups which confer this power, such as —OH, are also auxochromic in Witt's sense and thus the term auxochrome is often and very confusingly used in a second sense, a group which enables the dye to adhere to the fabric.

The nature of the combination between the dye and the material dyed is not the same with all materials.[1] With some substances, such as wool, there is chemical combination, but an artificial silk made of cellulose acetate contains no reactive groups which can combine chemically with the dye, and dyeing is a process of preferential solution of the dye in the fibre. Hence dyes for cellulose acetate silk are coloured compounds which are sparingly soluble in water, so that in the dye bath the dye goes into solution in the fibre in which it is more soluble. The azo dyes used for such silks are simple amino-azo compounds such as Me—⟨◯⟩—N : N—⟨◯⟩—NH$_2$. If the dye contains groups which increase its solubility in water, it is of little use for cellulose acetate. There is, however, the difficulty of getting any depth of shade when the dye is only slightly soluble in the dye bath. An ingenious method of overcoming this difficulty was devised by A. G. Green.[2] A primary or secondary amino group of an aminoazo compound combines with the bisulphite compound of formaldehyde, and the product is a sulphonic acid and thus readily soluble in water. It is, however, hydro-lysed by dilute acids and alkalis, and the dye-stuff separates out. Conse-quently acetate silk can be dyed by immersing it in the solution and adding dilute acid, when the dye, as it slowly separates, is taken up by the silk.

$$—NR \cdot CH_2 \cdot SO_3H + H_2O \longrightarrow —NRH + CH_2(OH) \cdot SO_3H$$

With the other common fabrics, wool, natural silk and cotton, the mechanism of dyeing is more complicated. Preferential solubility of the dye in the fibre plays some part, especially with certain dyes, but true chemical combination is a more important factor and to a less extent adsorption of the dye on the surface of the fibre. The animal fibres, silk and wool, are composed of protein material and contain basic groups; the ease with which they absorb dyes containing one or more sulphonic acid groups seems to be connected with direct union of the basic fibre with the acid dye. This is shown by the fact that a fixed weight of either silk or wool absorbs amounts of different acid dyes which are directly proportional to the equivalent weights of the dyes as acids.[3]

The enormous range of azo dyes exemplifies all the more important methods of dyeing silk, wool, and cotton, with the exception of dyeing from a vat with a vat dye-stuff, of which indigo is the prototype (see p. 507). The simpler hydroxy- and amino-azo compounds, which are only very

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[1] An interesting discussion of the physics and chemistry of dyeing by K. H. Meyer will be found in *Naturwiss.* 1927, 15, 129.

[2] The 'Ionamine' dyes; A. G. Green and K. H. Saunders, *J. Soc. Dyers and Colour.* 1923, 39, 10.   [3] K. H. Meyer, loc. cit.

sparingly soluble in water, are not absorbed by these fabrics from aqueous solution. They are, nevertheless, used as dyes, the final stage of the preparation of the coloured compound being carried out on the fabric itself. These compounds are called 'ingrain' colours or, because ice is needed for the diazotization stage of the dyeing process, 'ice' colours. A simple example is Para Red. The fabric is treated with a solution of β-naphthol which it absorbs: it is then passed through a bath containing diazotized p-nitroaniline, when coupling takes place and the dye-stuff p-nitrobenzene-azo-β-naphthol is formed in the fibre. The colour is cheap and reasonably permanent and has been much used for cotton. A more important example is Naphthol AS and its derivatives, which were introduced in 1911. The substance itself is 2,3-hydroxy-naphthoic anilide (I), and, as indicated

I.   II.   III.

below, it combines very readily with cotton in virtue of the anilide group. It can be coupled with various diazo compounds to give a large number of shades. Naphthol AS can be replaced by a variety of its substitution products, and by combining these compounds with the various diazo compounds a range of colours from yellow to blue can be obtained. They are excellent for cotton, but not used for wool.

The larger number of azo dyes are sulphonic acids and are thus water-soluble. The simpler compounds are absorbed by the animal fibres, wool and silk, and combine with the protein matter, but will not combine with the purely carbohydrate fibre of cotton unless it has been previously mordanted, usually with tannic acid. They belong to the class of 'acid dyes' because they are all acidic in character. The compounds which have been most used contain two or more azo groups, and are mostly naphthalene derivatives. A series of amino-naphthol sulphonic acids are known to which trade names such as S acid (II) and J acid (III) are given, and these can be coupled first in acid solution when an azo group enters the ortho position to the amino group, and then again in alkaline solution where another azo group is produced ortho to the hydroxyl group. Different amines can be used for each coupling and the final dye-stuff can be diazotized and coupled with another component to form a trisazo dye, so that in the continuous search for new dyes of valuable properties, fastness, shade, &c., compounds of great complexity have been synthesized. A short inspection of the *Colour Index* (Bradford, 1924) with its pages of azo dyes, many bearing nine or ten different trade names, will illustrate this point.

It was found that certain of the compounds so prepared have the power of dyeing cotton without a mordant (substantive dyes). These compounds

form the important class of direct cotton colours or 'salt colours', because inorganic salts such as sodium sulphate are added to the dye bath to aid the absorption of the dye by the fibre. This property of dyeing cotton seems to be conferred by the presence of certain groups in the molecule; it is shown by compounds which contain a urea residue —NH·CO·NH—, usually obtained by the action of phosgene, $COCl_2$, on an amino compound; by anilides containing the group —NH·CO·Ar; by derivatives of p-diamines such as p-phenylene-diamine; and by those of benzidine NH_2—◯—◯—NH_2, as well as certain others. The benzidine derivatives are probably the most important. Two examples will be selected from the enormous number of variations which are possible and have been used. Amino-cresotinic acid is converted into its p-nitrobenzoyl derivative, the nitro group is reduced, and the resulting amino group diazotized and coupled with p-amino-benzoyl-J acid. The resulting dye, Diazo Light Scarlet 5BI (IV), can be diazotized and coupled ('developed') with β-naphthol in the fibre and is very fast to light and washing.

IV.

A dye which has been used for black sewing cotton, Zambesi Black V, is made by combining p-nitraniline with α-naphthylamine-7-sulphonic acid, reducing the product, diazotizing it and coupling with the substance obtained from S-acid and p-nitraniline, and finally reducing the nitro group. The formula is shown below, the names indicating the components. After dyeing, the compound, which already contains three azo groups, is developed with β-naphthol on the fibre.

| p-Nitraniline | Cleve Acid | S-Acid | p-Nitraniline |

The last class of azo dyes that will be mentioned are the mordant dyes which contain a metal, usually chromium or copper. These contain hydroxyl groups in the ortho position to a carboxyl group or an azo group so that co-ordination compounds are formed with metals, just as salicylic acid gives a deep violet colour with ferric iron.[1] In some cases the fabric

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[1] See N. V. Sidgwick, *Electronic Theory of Valency*, p. 234 et seq.

is allowed to absorb the dye and is afterwards treated with a suitable compound of the metal, but in others the metallic complex is soluble in water and can be dyed straight on to the fabric. They are used for wool and give extremely fast colours.

The Nitrosamines

The nitrosamines are compounds in which the nitroso group —NO is attached to nitrogen. For reasons which are obscure the properties which are typical of this group in the compounds where it is attached to carbon are not shown in the nitrosamines. They do not tend to form double molecules nor are any of them blue or green in colour. The great majority of the nitrosamines are obtained from secondary amines and other compounds containing the —NH— group by the action of nitrous acid. Primary nitrosamines, i.e. compounds derived from primary amines and containing the group —NH·NO, are almost unknown. As we have seen, the action of nitrous acid on aliphatic amines gives either an alcohol or an aliphatic diazo compound, while the usual product from an aromatic primary amine is a diazonium salt. The only primary nitrosamines known are unstable compounds obtained from isodiazohydrates, and these have been mentioned on p. 421. The nitrosamines can be divided into two classes, those derived from secondary amines and those derived from amides and hence containing an acyl group, e.g. $\phi \cdot CO \cdot N(NO) \cdot Me$.

All basic secondary amines if dissolved in a mineral acid and treated with nitrous acid, usually by addition of sodium nitrite, give nitrosamines of the general formula $RR'N \cdot NO$. In the aliphatic series the rate of formation of dimethylnitrosamine from dimethylamine and nitrous acid in aqueous solution has been measured,[1] and the reaction has been found to involve the amine kation, the nitrite ion, and an undissociated molecule of nitrous acid; the same reaction complex is involved as in the reaction between a primary aliphatic amine and nitrous acid, but it breaks up into the nitrosamine and nitrous acid. The rate of reaction is necessarily diminished by excess of a mineral acid because the concentration of the nitrite ion is reduced. With aromatic secondary amines, however, excess of acid seems to have little effect, and the reaction is almost certainly between the amine kation and undissociated nitrous acid, as in the process of diazotizing a primary aromatic amine (see p. 402). In both cases, of course, the reaction can be represented by the equation

$$RR'NH + HONO \longrightarrow RR'N \cdot NO + H_2O.$$

The simple aliphatic nitrosamines are yellowish liquids which boil without decomposition ($Me_2N \cdot NO$, boiling-point 149°; $Et_2N \cdot NO$, boiling-point 177°). They are soluble in water, but can be salted out of aqueous solution with potassium carbonate. They show only very weakly basic properties; a hydrochloride of dimethylnitrosamine is formed by passing hydrogen chloride into its ethereal solution, but the salt is completely

[1] T. W. J. Taylor and L. S. Price, *J.C.S.* 1929, 2052.

decomposed by alcohol and water. The simple aromatic nitrosamines, such as methylphenylnitrosamine, which is readily obtained from methyl aniline, are low-melting solids or yellowish oils of a characteristic and somewhat nutty smell. They are insoluble in water and can be distilled under reduced pressure, although under atmospheric pressure they undergo decomposition. They are as weakly basic as the aliphatic compounds. The structure of the nitrosamines is shown by the fact that they can be reduced by weak reducing agents such as zinc and acetic acid to unsymmetrically di-substituted hydrazines: $RR'N \cdot NO \longrightarrow RR'N \cdot NH_2$. With a more powerful agent such as tin and hydrochloric acid they are reduced to the secondary amine from which they are derived:

$$RR'N \cdot NO \longrightarrow RR'NH.$$

In the presence of strong hydrochloric or hydrobromic acid the nitrosamines are unstable. The aliphatic compounds can be converted almost quantitatively into nitrous acid and the secondary amine by boiling with hydrochloric acid, the reversal of their method of formation. In some cases nitrosyl chloride can be detected in the products, and it is possible that the reaction is simply $RR'N \cdot NO + HCl \longrightarrow RR'_2NH + NOCl$, the nitrosyl chloride usually being hydrolysed to nitrous acid or its decomposition products. With aromatic nitrosamines the behaviour with hydrochloric acid is more complicated. There is the same fission to the secondary amine and nitrous acid or one of its derivatives, and possibly an equilibrium is set up. Certainly in the presence of a reagent such as urea or thio-urea, which can react rapidly with nitrous acid, the nitrosamine is converted quantitatively into the secondary amine,[1] and the nitroso group is eliminated quantitatively as nitric oxide if a nitrosamine in hydrochloric acid is treated with cuprous chloride or ferrous chloride:[2]

$$\phi \cdot NMe \cdot NO + HCl + CuCl(FeCl_2) \longrightarrow \phi \cdot NHMe + NO + CuCl_2(FeCl_3).$$

If, however, such a reagent is absent, the nitrous acid or derivative can attack the aromatic nucleus and the product may contain the p-nitroso secondary amine. This is the so-called Fischer-Hepp transformation:[3] if an aromatic nitrosamine is allowed to stand at room temperature with a solution of hydrogen chloride in a mixture of alcohol and ether, the nitroso group appears to migrate to the carbon atom in the para position to the amino group, and the hydrochloride of the C-nitroso compound slowly crystallizes out. Thus methylphenylnitrosamine gives p-nitrosomethyl aniline:

There is little doubt that this reaction like many similar transformations is not an intramolecular rearrangement but occurs in two stages, the first

[1] W. G. Macmillan and T. H. Reade, *J.C.S.* 1929, 585.

[2] K. Lehmstedt, *Ber.* 1927, **60**, 1910; E. C. S. Jones and J. Kenner, *J.C.S.* 1932, 711.   [3] O. Fischer and E. Hepp, *Ber.* 1886, **19**, 2991.

of which consists in fission between the nitrogen atoms by the acid to give the secondary amine, and the second is the nitrosation of the amine.[1] The fact that alcoholic sulphuric acid will not bring about the rearrangement shows that the hydrogen chloride or bromide plays a specific part in the reaction, probably by producing the nitrosyl halide which reacts with the p-carbon atom. The reaction is hence not a rearrangement of the nitrosamine kation.

The ready formation of a nitrosamine from a secondary amine affords a convenient method for separating such an amine from a mixture with primary and tertiary amines. The primary are decomposed by nitrous acid and the tertiary are unaffected. The nitrosamine is not basic and can be separated easily from the basic tertiary amine; the secondary amine is recovered from the nitrosamine by one of the methods already mentioned, either reduction or boiling with hydrochloric acid in the presence of urea.

A nitrosamine can always be detected by Liebermann's reaction. This consists in warming the substance with phenol in concentrated sulphuric acid when a red solution is formed which turns to blue when it is diluted with water and made alkaline with caustic soda. The blue colour is due to the formation of the sodium salt of an indophenol which is formed by the union of p-nitrosophenol with phenol.[2]

This colour reaction is given by nitrous acid and all compounds which are broken down to nitrous acid by sulphuric acid. Many, but not all, of the C-nitroso compounds also show this reaction.

The second class of compounds of the general formula $RR'N \cdot NO$ consists of those containing an acyl group and derived from the amides. They are called nitrosamides and have the general formula $R \cdot CO \cdot NR' \cdot NO$. The best known are the nitroso derivatives of the anilides, e.g. nitrosoacetanilide, $CH_3 \cdot CO \cdot N(NO) \cdot \phi$. These compounds resemble the true nitrosamines in some respects, but in most of their reactions, owing to the ease with which the acyl group splits off, they behave like aromatic diazo compounds. They can be obtained by the action of nitrous fumes on an anilide in glacial acetic acid and also by the action of an acid anhydride on a diazotate:

$$CH_3 \cdot CO \cdot NH\phi \longrightarrow CH_3 \cdot CO \cdot N(NO) \cdot \phi \longleftarrow \phi \cdot N:NONa + (CH_3 \cdot CO)_2O.$$

They are unstable and reactive solids which usually explode on rapid heating and decompose on standing. Like the true nitrosamines, they are decomposed by hydrogen chloride in an inert solvent to the anilide from which they are derived and nitrosyl chloride. But just as an amide can be hydrolysed while an amine cannot, so in the majority of reactions the acyl group is lost, and the behaviour is that of a diazo compound.

[1] See J. Houben, ibid. 1913, **46**, 3984.

[2] H. Decker and B. Solonina, ibid. 1902, **35**, 3217.

The simplest example is the action of caustic alkalis, which gives the diazotate:

$$CH_3 \cdot CO \cdot N(NO) \cdot \phi + 2NaOH \longrightarrow CH_3 \cdot CO_2Na + \phi \cdot N:NONa + H_2O.$$

Some of the reactions they show are rather surprising; if a benzene solution of nitrosoacetanilide is left to stand at room temperature, nitrogen is lost and diphenyl is formed;[1] and from a solution in toluene, o- and p-phenyltoluene can be obtained.

$$CH_3 \cdot CO \cdot N(NO) \cdot \phi + C_6H_6 \longrightarrow CH_3 \cdot CO_2H + N_2 + C_6H_5 \cdot C_6H_5$$

They will also couple with phenols and amines just like diazo compounds. This similarity to the diazo compounds was one of the reasons which prompted Angeli to put forward the view that the isomeric diazotate and isodiazotate should be given the structures $Ar \cdot NO:NNa$ and $Ar \cdot N:NONa$, respectively. His suggestion has not, however, received general acceptance because it is incapable of extension to the diazocyanides which contain no oxygen (see p. 418).

Other Compounds Containing Two Linked Nitrogen Atoms

The only two sets of compounds belonging to this class which will be mentioned are the nitramines and the isomeric nitrosohydroxylamines. The former contain a nitro group attached to nitrogen, and the formula of phenylnitramine is shown in (Ia) and (Ib) with the nitro group in its normal and *aci*-forms, while in the latter a nitroso group is attached to nitrogen, and the two possible forms of nitrosophenylhydroxylamine can be represented by formulae (IIa) and (IIb).

$\phi \cdot NH \cdot N:O$	ϕ—N:N—OH	$\phi \cdot N \cdot NO$	$\phi \cdot N:NOH$
$\downarrow$	$\downarrow$	$\mid$	$\downarrow$
O	O	OH	O
Ia.	Ib.	IIa.	IIb.

The isomerism of the compounds, especially if written as (Ib) and (IIb), recalls that of the isomeric azoxy compounds (see p. 428), and has been used by Angeli to support his views on the structure of the diazotates which have been referred to.

The primary nitramines are acidic like the primary and secondary aliphatic nitro compounds (see p. 231). There is little doubt that the salts are derived from an *aci*-form such as (Ib). Aliphatic nitramines can be obtained from the urethanes (see p. 273). These are nitrated on the nitrogen atom by concentrated nitric acid and the product when treated with ammonia gives the ammonium salt of the nitramine.

$$CH_3 \cdot NH \cdot CO_2Et \longrightarrow CH_3 \cdot N(NO_2) \cdot CO_2Et \longrightarrow CH_3 \cdot N:NO \cdot ONH_4$$

The primary aromatic nitramines are best prepared by the oxidation of an aromatic diazotate, usually with alkaline ferricyanide. After the oxidation the free nitramine is precipitated by cautious addition of

[1] E. Bamberger, *Ber.* 1897, **30**, 366.

sulphuric acid.[1] They are also formed by treating a diazonium per-
bromide with alkali, when the hypobromite formed oxidizes the diazotate.

Aromatic secondary nitramines are formed in the vigorous nitration of
certain secondary amines. Thus methylaniline is converted into a tetra-
nitro compound in which three nitro groups are attached to the nucleus
and one to the amino group. The same product, 2,4,6-trinitro-phenyl-
methylnitramine, is obtained from dimethylaniline, one methyl group
being replaced by a nitro group. This compound, which is called 'Tetryl',
has been used as an explosive.

Phenylnitramine is a solid which melts at 46° and explodes if heated
rapidly. It is slightly soluble in water and gives an acid solution; it is
sometimes called diazobenzolic acid. It is an electrolyte in aqueous solu-
tion, but in benzene it only slowly forms an ammonium salt with dry
ammonia, and thus would appear to be the true nitro form (Ia) in benzene
and a tautomeric mixture of the normal and aci-form in water.[2] It can be
reduced to sodium benzene isodiazotate with sodium amalgam and then
further to phenylhydrazine. It is very sensitive to acids and in their
presence the nitro group appears to migrate from the amino group to the
nucleus, as is often the case with N-substituted anilines. This case is,
however, exceptional; the main product is not the para compound, but
ortho-nitraniline together with small amounts of the para compound,
while in the majority of other apparent migrations of this type the reverse
is true. The reaction has been examined by A. E. Bradfield and K. J. P.
Orton[3] and is quite different from the transformation of N-chloroaniline
into p-chloroaniline. In the latter case there is direct evidence that the
catalysing acid liberates chlorine from the N-chloro compound which then
enters the para position to the amino group in the ordinary way. The
transformation of the nitramine, however, gives various by-products as
well as the nitranilines, and several simultaneous reactions take place
which are difficult to sort out. One of these seems to be a true intramole-
cular rearrangement, which does not occur with N-chloroaniline, and it is
possible that the exceptional formation of so much of the ortho product
(o-nitraniline) is due to this.

Nitrosophenylhydroxylamine (IIa and b) is formed by the action of
nitrous acid on N-phenylhydroxylamine,

$$\phi \cdot NHOH \longrightarrow \phi \cdot N(NO) \cdot OH.$$

It is sometimes very confusingly called an isonitramine, but since the
prefix iso is used to describe an aci-nitro compound such as (Ib), this name
should be avoided. It is also formed in a curious reaction between nitro-
benzene and hydroxylamine in the presence of sodium ethoxide.

$$\phi \cdot NO_2 + NH_2OH \longrightarrow \phi \cdot NO:NOH$$

It is a solid melting at 59° and decomposing at 75°, and is not at all stable.
It is decomposed by dilute acids or mild oxidizing agents with formation of

[1] E. Bamberger, ibid. 1894, **27**, 363.
[2] A. Hantzsch and F. E. Dollfus, ibid. 1902, **35**, 258.   [3] *J.C.S.* 1929, 915.

nitrosobenzene. It is a true acid forming an ammonium salt immediately with dry ammonia in benzene, but it is not known which of the two possible structures (II *a* and *b*) the free substance possesses.

The ammonium salt of this compound is a well-known reagent in inorganic analysis and is known by the name 'cupferron'. It is prepared by treating a solution of N-phenylhydroxylamine with dry ammonia and an alkyl nitrite, when the reagent crystallizes out.[1] The arrangement of the atoms in the molecule is clearly adapted for the formation of co-ordination complexes with metals, because there is a hydroxyl group containing a replaceable hydrogen atom and also an oxygen atom so placed that it can form a co-ordinate link to the metal as in (III): the number of links formed depends, of course, on the valency of the metal. The five-membered

ring recalls that in the metallic derivatives of certain of the oximes (p. 196). The metallic complexes derived from cupferron are not stable enough to be dried and weighed as such, but because of the differences in solubilities between the complexes of various metals cupferron is valuable for carrying out certain separations. It was first used for copper and iron,[2] whence its name is derived, but it has proved useful for titanium, uranium, and other metals as well.

Note on the cis *Form of Azobenzene.* G. S. Hartley observed that solutions of azobenzene in acetone became more strongly absorbing on exposure to light.[3] The new stereo-isomer responsible for the change was isolated from such solutions by adding water, filtering, and extracting the filtrate with light petroleum to remove the *trans* form, and then with chloroform. The melting-point of *cis*-azobenzene, 71·4°, falls on repeated fusion to a eutectic at 41° and then rises to 68°, the melting-point of *trans*-azobenzene. After irradiation, solutions of azobenzene contain 15–40 per cent. of the *cis* form, depending on the solvent. *Cis*-azobenzene is more soluble in water and less soluble in benzene than the *trans* form, in agreement with the polar character of *cis*-azobenzene which has a dipole moment of 3·0 D,[4] compared with the zero moment of the *trans* compound. The heat of conversion of the solid *cis*- into the solid *trans*-azobenzene is 12 kilogram calories per gram molecule. Crystallographic examination shows that the *trans* form is almost planar and centrosymmetrical, but that in the *cis* form the benzene rings are not coplanar.[5]

The separation of *cis*-azobenzene from irradiated solutions is more simply achieved by chromatographic adsorption on an alumina column, and this method has been applied successfully to other azo compounds.[6] *Cis*-azobenzene is much more strongly adsorbed on alumina than the *trans* isomer.[7]

[1] *Organic Syntheses*, Collective vol. 1, New York, 1932, p. 171.

[2] O. Baudisch, *Zent.* 1910, i, 684.   [3] *Nature*, 1937, **140**, 281; *J.C.S.* 1938, 633.

[4] Hartley and R. J. W. Le Fèvre, *J.C.S.* 1939, 531.

[5] J. M. Robertson, ibid. 1939, 232.   [6] A. H. Cook, ibid. 1938, 876; 1939, 1309; L. Zechmeister, O. Frehden, and P. F. Jörgensen, *Naturwiss.* 1938, **26**, 495.

[7] For an account of chromatographic adsorption methods see *Principles and Practice of Chromatography*, L. Zechmeister and L. Cholnoky, English trans., 1941.

COMPOUNDS CONTAINING A CHAIN OF THREE OR MORE NITROGEN ATOMS

OF the compounds belonging to this class the derivatives of hydrazoic acid have been dealt with already (Chap. XI) because of their close relationship to the aliphatic diazo compounds. There are not many which remain for discussion because nitrogen, unlike carbon, shows little tendency to form stable chains, as the properties of the compounds described in this chapter will indicate. As the number of linked nitrogen atoms increases, so the compounds in general become more unstable and often explosive. The compounds can be classified according to the number of nitrogen atoms in the chain and are regarded as derivatives of the hypothetical compounds of nitrogen and hydrogen, triazane, $NH_2 \cdot NH \cdot NH_2$, tetrazane, $NH_2 \cdot NH \cdot NH \cdot NH_2$, and so on, unsaturation in the nitrogen chain being denoted by the ending -ene, as with the carbon compounds. Curtius proposed the names prozane and buzane for triazane and tetrazane on the analogy with propane and butane, but this nomenclature is seldom used.

Diazoamino Compounds

The best known of the three-nitrogen compounds, apart from the azides, are triazene derivatives of the general formula $R \cdot NH \cdot N : N \cdot R'$. The aromatic members of this class have been known for a long time and are usually called diazoamino compounds. Thus $\phi \cdot NH \cdot N : N \cdot \phi$ is referred to as diazoamino-benzene. As with the azo compounds, purely aliphatic, mixed aliphatic-aromatic, and purely aromatic compounds are known and their stability and also their colour increase in that order. All triazene compounds are decomposed by acids, the nitrogen chain being broken and an amine splitting off: the sensitivity to acids is very marked with the aliphatic compounds and least of all with the aromatic compounds. The other fragment of the molecule is probably in all cases a diazonium salt, which can be isolated from the aromatic compounds, but in the aliphatic and the mixed series the diazonium salts do not exist, so that their decomposition products alone can be observed. Thus 1,3-dimethyltriazene is very easily decomposed by hydrochloric acid to methylamine, methyl chloride, and nitrogen, while the aromatic compounds give with hydrogen chloride the diazonium chloride and the amine.

$$Me \cdot N : N \cdot NH \cdot Me + HCl \longrightarrow MeCl + N_2 + H_2N \cdot Me$$
$$Ar \cdot N : N \cdot NHR \longrightarrow Ar \cdot N_2Cl + H_2N \cdot R$$

These triazene derivatives are amphoteric in that the hydrogen atom attached to nitrogen is replaceable by metals, while those which are comparatively stable to acids also form hydrochlorides with hydrogen chloride

in dry benzene. The diazoamino compounds are extremely weak both as acids and as bases, and their salts of both kinds are decomposed by water.

There is one reaction whereby diazoamino compounds of all types can be obtained—the action of an organo-magnesium halide on an azide.[1]

$$R \cdot N_3 + R'MgBr \longrightarrow R \cdot N(MgBr) \cdot N:N \cdot R' \longrightarrow R \cdot NH \cdot N:N \cdot R'$$

This is the only method of preparation for the little-known dimethyl-triazene, $Me \cdot N:N \cdot NH \cdot Me$, but the compound is so sensitive to acids that its magnesium derivative cannot be treated with any acid, even carbonic acid, to liberate the free substance. Its separation is further complicated by the fact that it is soluble in water and volatile with ether vapour. Dimroth succeeded in obtaining it by treating the magnesium derivative with ammonium chloride, extracting the triazene with ether and obtaining the cuprous derivative, $MeN:N \cdot NCu \cdot Me$, with ammoniacal cuprous chloride. This cuprous compound could be purified by recrystallization from ether and was very ingeniously decomposed by grinding it with diazoamino-benzene, which is more strongly acidic and takes up the copper to set free dimethyltriazene. The latter is a colourless liquid which boils with some decomposition at 92° and explodes when it is heated rapidly. Its aqueous solution is alkaline but it does not form salts with acids because it is decomposed even by the weakest of them.

The mixed aromatic-aliphatic diazoamino compounds can be prepared in a similar way, but their separation is easier, because they are less soluble in water and not so volatile. They are also formed by coupling aromatic diazo compounds with aliphatic amines, best in weakly alkaline solution. This reaction gives good yields with secondary amines such as dimethyl amine, when the product is an aryl-dimethyltriazene of the formula $\phi \cdot N:N \cdot NMe_2$. With a primary aliphatic amine the main product is formed by the coupling of two diazo residues with one molecule of amine and belongs to the class of bisdiazoamino compounds which are discussed below, but a small amount of the diazoamino compound is formed as well. The mixed diazoamino compounds are liquids or low-melting solids which decompose on standing with acids to give the aromatic amine and the decomposition products of the aliphatic diazonium salt:

$$\phi \cdot N:N \cdot NHMe + H_2O \longrightarrow \phi NH_2 + MeOH + N_2.$$

The first aromatic diazoamino compound was obtained by P. Griess shortly after his discovery of the aromatic diazo compounds. These compounds can be obtained from the azides, but are usually prepared by the interaction of a diazo compound with a primary aromatic amine; the tendency to form bisdiazoamino compounds is much smaller than with primary aliphatic amines.

$$\phi \cdot N:NOH + H_2N\phi \longrightarrow \phi \cdot N:N \cdot NH \cdot \phi$$

[1] O. Dimroth, *Ber.* 1903, **36**, 909.

This coupling reaction takes place very readily in neutral or weakly acid solution, so that they are often inadvertently formed in the diazotization of an aromatic amine when the solution does not contain sufficient mineral acid. The ordinary method of preparing diazoamino-benzene is to add to a solution of aniline in hydrochloric or sulphuric acid sufficient sodium nitrite to diazotize half the aniline, and then to treat with excess of sodium acetate, when the hydrogen-ion concentration is reduced to the point where the diazobenzene reacts with the unchanged aniline. Some secondary amines can also couple with diazo compounds, but in many cases with both primary and secondary amines the coupling takes place with a carbon atom of the aromatic ring and no diazoamino compound can be isolated (see p. 410). Whether C-coupling or N-coupling predominates is determined in other cases by the conditions, but no generalization seems possible. The aromatic diazoamino compounds are yellow or brownish yellow solids insoluble in water and dilute acids and alkalis, and are more stable than the other classes: this probably is connected with con-jugation of the unsaturation of the nitrogen atoms with the aromatic nuclei. They usually have definite melting-points and decompose at slightly higher temperatures, sometimes with a weak explosion. Their mercury and copper derivatives, unlike the sodium salts, are not decom-posed by water, and are probably covalently linked compounds. The cuprous derivative can be obtained by the action of an alcoholic solution of a diazoamino compound on copper powder.

All attempts to reduce a diazoamino compound to the saturated triazane, $Ar \cdot NH \cdot NH \cdot NH \cdot Ar$, have failed; the products are usually an amine and a hydrazine:

$$Ar \cdot NH \cdot N : N \cdot Ar \longrightarrow Ar \cdot NH_2 + H_2N \cdot NHAr.$$

If diazoamino-benzene is treated with hydrogen bromide in dry ether, aniline hydrobromide and benzene diazonium bromide are formed, but under other conditions treatment with acids results in a mixture of pro-ducts coming from the decomposition of the diazo compound. The most interesting reaction of these compounds is their conversion into amino-azo compounds (see p. 445). If diazoamino-benzene is dissolved in aniline with a small amount of aniline hydrochloride, and the mixture kept warm for a short time, it is converted in very good yield into p-amino-azobenzene.

$$\phi N : N \cdot NH\phi \longrightarrow \phi \cdot N : N \text{—}\left\langle\ \right\rangle\text{—} NH_2$$

The reaction is common to all the compounds which have a free para position and to many in which the ortho position is free, although in these cases it takes place less readily. This reaction has often been considered to be an intramolecular rearrangement, the group $\phi \cdot N : N$— migrating from the nitrogen atom to the para position, but, as in many of these postulated rearrangements, all the evidence is against such a view and indicates that it is a two-stage process. In the first stage the diazoamino

compound is split up by the hydrogen chloride into aniline and the diazonium chloride, and the second stage consists of the reaction between these two to give the amino-azo product.

$$\phi N:N\cdot NH\phi \longrightarrow \phi N_2Cl + \langle\ \rangle - NH_2 \longrightarrow \phi\cdot N:N - \langle\ \rangle - NH_2$$

The transformation does not take place except in the presence of acids or easily hydrolysed salts such as zinc chloride.[1] If, instead of the usual conditions of aniline as solvent with aniline hydrochloride, dimethylaniline and its hydrochloride are substituted, the main product is dimethylamino-azobenzene,[2] $Me_2N\cdot C_6H_4\cdot N:N\cdot\phi$, a fact which is inexplicable on the rearrangement theory, but would be expected from the coupling of benzene diazonium chloride with the dimethylaniline, which is present in excess. Finally, if an inert solvent is used instead of aniline, the yield is not so good because a certain amount of benzene diazoamino-azobenzene,

$$\phi\cdot N:N\cdot C_6H_4\cdot NH\cdot N:N\cdot\phi,$$

is formed, and this clearly comes from the coupling of benzene diazonium chloride with undecomposed diazoamino-benzene.[3] The presence of excess of aniline prevents the formation of this compound because there is plenty of aniline with which coupling can take place. It is known that whether C-coupling or N-coupling occurs depends largely on the acidity of the solution, the former being favoured at higher hydrogen-ion concentration. The transformation of diazoamino-benzene into amino-azobenzene is the decomposition of the diazoamino compound into aniline and a benzene diazonium salt under the right conditions of acidity for the two to couple to the C-azo product.

The next point that demands attention is the tautomerism of the diazo-amino compounds. The structure suggests that if a substituent were introduced into one of the nuclei of diazoamino benzene, two isomeric compounds might occur, $\phi\cdot N:N\cdot NH\cdot C_6H_4X$ and $\phi\cdot NH\cdot N:N\cdot C_6H_4X$. No such isomerism is known. If benzene diazonium chloride reacts with p-toluidine, the product is identical with that obtained from toluene diazonium chloride and aniline. Further, if this one compound is reduced, it gives aniline, p-toluidine, phenylhydrazine and p-tolylhydrazine. The latter evidence is, however, of doubtful value, since if the reduction proceeds via the triazane, $\phi\cdot NH\cdot NH\cdot NH\cdot C_6H_4X$, four reduction products might be expected even if the diazoamino compound were not tautomeric. In solution the substance behaves as a tautomeric mixture:

$$Me\cdot C_6H_4\cdot N:N\cdot NH\cdot\phi \rightleftharpoons Me\cdot C_6H_4\cdot NH\cdot N:N\cdot\phi.$$

Similarly if an unsymmetrical diazoamino compound is alkylated, two N-alkyl compounds are formed, each of which can be obtained separately

[1] E. Rosenhauer, *Ber.* 1930, **63**, 1056.
[2] E. Rosenhauer and H. Unger, ibid. 1928, **61**, 392.
[3] J. C. Earl, *Proc. Roy. Soc., New South Wales*, 1929, **63**, 89.

by coupling the appropriate diazo compound with the appropriate secondary amine.[1]

$$Ar \cdot N : N \cdot NH \cdot Ar' \; \rightleftharpoons \; Ar \cdot NH \cdot N : N \cdot Ar'$$
$$\downarrow \qquad\qquad\qquad\qquad \downarrow$$
$$Ar \cdot N : N \cdot NMe \cdot Ar' \; + \quad Ar \cdot NMe \cdot N : N \cdot Ar'$$

These facts, of course, are not surprising: the nitrogen chain with one hydrogen atom and one double bond is very similar to many other triad systems in which tautomerism occurs. Two questions, however, remain. The first is the position of the equilibrium between the tautomers in any given case, and the second is the actual structure of the solid compound, which may be either of the two possible tautomers or a solid solution of the two. There has been much discussion of the first point and conflicting views have been advanced, but the arguments used rest on assumptions that have not been proved. If we have a mixture of two tautomers and allow them to react with some substance which will give different products with the two, there is no justification for assuming that the proportions in which the two products are formed is any indication of the proportions of the two tautomers in the original mixture. The tautomers will not necessarily react with the reagent at the same rate, and if one is removed by the reaction faster than the other, the tautomeric equilibrium is upset. If now the rate of tautomeric change is at all appreciable under the conditions used, more of the first tautomer will be formed from the second and will react with the reagent. Thus, if the rate of tautomeric change is high and the tautomers differ widely in their respective rates of reaction with the third substance, it is possible to have a case where the product is almost entirely derived from a tautomer which is present in only a very small amount in the original mixture. Alteration of temperature may alter the proportion in which the two products are formed, not by altering the equilibrium between the tautomers, but by having a different effect on the velocity constants involved. In the present case of the unsymmetrical diazoamino compounds we have no knowledge of the rate of tautomeric change, and so can only guess at the position of equilibrium between the tautomers.

The last triazene compound that will be mentioned contains only one carbon radical. If phenylazide is reduced with stannous chloride and dry hydrogen chloride in absolute ether at $-20°$, phenyltriazene, $\phi \cdot N : N \cdot NH_2$, is formed. Its separation from the reaction mixture is difficult, but it can be purified through its copper derivative which is then decomposed with aqueous potassium cyanide at a low temperature.[2] It forms colourless leaflets which melt at 50° and is extremely unstable. It rapidly decomposes into aniline and nitrogen in all solvents at room temperature.

$$\phi \cdot N : N \cdot NH_2 \; \longrightarrow \; \phi \cdot NH_2 + N_2$$

Attempts to prepare the reduction product of this compound, phenyl triazane, $\phi \cdot NH \cdot NH \cdot NH_2$, have been unsuccessful. If a urea derivative

[1] See, e.g., C. Smith and C. H. Watts, *J.C.S.* 1910, **97**, 562.
[2] O. Dimroth, *Ber.* 1907, **40**, 2378.

is treated with sodium hypobromite, a hydrazine derivative is formed by a Hofmann reaction (p. 379): $\phi \cdot NH \cdot CO \cdot NH_2 \longrightarrow \phi \cdot NH \cdot NH_2$. Therefore A. Darapsky[1] attempted to prepare phenyl triazane in a similar way from phenyl semicarbazide: $\phi \cdot NH \cdot NH \cdot CO \cdot NH_2 \longrightarrow \phi \cdot NH \cdot NH \cdot NH_2$. The only products formed, however, were phenyl azide, resulting presumably from the oxidation of the triazane, and nitrogen.

Tetrazane Derivatives

Two series of derivatives are known which contain a saturated chain of four nitrogen atoms. The first consists of the hexa-substituted tetrazanes: our knowledge of their startling properties is due to Stefan Goldschmidt and his pupils.[2] The second series have the general formula

$$RCH:N \cdot NR' \cdot NR' \cdot N:CHR$$

and are often called hydrotetrazones.

The best known of the hexa-substituted tetrazanes are the aryl derivatives such as the hexaphenyl compound $\phi_2 N \cdot N\phi \cdot N\phi \cdot N\phi_2$, but this compound has this constitution only as a solid at low temperature. In solution it partially dissociates into the free radical triphenylhydrazyl, $\phi_2 N \cdot N\phi$—, which contains divalent nitrogen and is similar to the radicals formed in the spontaneous dissociation of the tetra-aryl hydrazines (see p. 388). The method of obtaining compounds of this type is the oxidation of tri-substituted hydrazines, $RR'N \cdot NH \cdot R''$, usually with lead peroxide in an inert solvent and sometimes with potassium ferricyanide. The first product of the oxidation is the hydrazyl free radical which shows its presence by its dark blue, green or violet colour. The fate of the hydrazyl depends on the nature of the substituents attached to the nitrogen atoms. If one is an acyl group such as acetyl or benzoyl, it polymerizes almost entirely to the tetrazane which can then be obtained as a colourless crystalline solid. In other cases the tetrazane is more difficult to obtain, because the equilibrium between hydrazyl and tetrazane lies on the side of the hydrazyl and the majority of the hydrazyl radicals are not very stable and enter into other reactions which are described below. Hexaphenyltetrazane can be obtained as a white solid by the oxidation of triphenylhydrazine, but all the operations must be performed at $-80°$. In solution it is blue because of the dissociation to the hydrazyl and the total depth of colour given by a fixed amount of the compound increases with the dilution which shows that the dissociation is greater at high dilutions. The solid itself turns green on warming to room temperature and loses its colour again on cooling, but neither as a solid nor in solution is the compound stable, and on standing the decomposition products of the hydrazyl are formed. The extreme case is the oxidation of α,α-diphenyl-β-trinitrophenylhydrazine, which can be obtained from diphenylhydrazine and picryl chloride. The free radical which is formed is much

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[1] *J. pr. Chem.* 1908, **76**, 433.

[2] *Ber.* 1920, **53**, 44; 1922, **55**, 616, 628; *Annalen*, 1924, **437**, 194; 1929, **473**, 137.

more stable than in the other cases and shows no tendency to polymerize to the tetrazane, so that the solid free radical can be obtained as deep violet crystals which look like potassium permanganate.

$$\phi_2N\cdot NH_2 + Cl\!-\!\!\underset{NO_2}{\overset{NO_2}{\bigcirc}}\!\!-\!NO_2$$

$$\longrightarrow\ \phi_2N\cdot NH\cdot C_6H_2(NO_2)_3\ \longrightarrow\ \phi_2N\cdot \underset{|}{N}\cdot C_6H_2(NO_2)_3$$

The magnetic moment of the solid has been measured[1] and shows clearly its free radical nature; the substance is paramagnetic and the value of the moment is that to be expected for a molecule containing an odd number of electrons. No alkyl tetrazanes of this kind are known. Dibenzyl-tert-butylhydrazine resists oxidation, and α,α-dibenzyl-β-picrylhydrazine is oxidized to the picrylhydrazone of benzaldehyde with loss of a benzyl group.

$$\underset{\phi CH_2}{\overset{\phi CH_2}{>}}N\cdot NH\!\!\underset{NO_2}{\overset{NO_2}{\bigcirc}}\!\!NO_2\ \longrightarrow\ \phi CH\!:\!N\cdot NH\!\!\underset{NO_2}{\overset{NO_2}{\bigcirc}}\!\!NO_2 + \phi CO_2H$$

The reactions of these tetrazanes in solution are those of the hydrazyls into which they are dissociated to a greater or lesser extent. Thus they combine with other free radicals such as triphenylmethyl and with nitric oxide. They are very readily reduced to the hydrazine from which they are derived and will remove hydrogen from hydroquinone, oxidizing it to quinone. Since the rate at which equilibrium is established between tetrazane and hydrazyl is quite small at low temperatures, the extent of dissociation can be measured by titrating rapidly with hydroquinone until the colour of the free radical has disappeared, and by this method the position of equilibrium at a series of temperatures has been determined in several cases; from the results the heat of dissociation of the tetrazane can be calculated, and varies from 7 to 18 kg. cals. per gram-molecule (the normal value of the heat of rupture of the N—N link is about 23 kg. cals.). The spontaneous decomposition of triphenylhydrazyl gives as main products diphenylamine and the diphenylhydrazone of quinone-anil,

$$\phi_2N\cdot N\!\!=\!\!\bigcirc\!\!=\!N\phi,$$

and these must result from a series of complicated changes. The hydrazyl radicals, unlike triphenylmethyl and its analogues, do not react with oxygen, but their decomposition is hastened by exposure to light. The tendency for these tetrazanes to dissociate is determined by the nature of

[1] E. Müller, L. Müller-Rodloff, and W. Bunge, ibid. 1935, **520**, 235; F. L. Allen and S. Sugden, *J.C.S.* 1936, 440.

the groups attached to the nitrogen atoms, but the relationships are more complicated than in the dissociation of hexa-arylethanes and tetra-arylhydrazines.[1] Usually, of course, the extent of dissociation depends on the solvent. The reasons underlying the existence of these radicals is much the same as those which have been mentioned above in the discussion of the radicals formed in the spontaneous dissociation of the tetra-aryl-hydrazines. The radicals are resonance-hybrids of a number of states in which various atoms in the molecule have a valency lower than the normal. The hydrazyl radicals are related to the tetra-arylhydrazine dissociation products in exactly the same way that pentaphenylethyl is related to triphenylmethyl.

The second class of tetrazane derivatives are somewhat confusingly sometimes called tetrazones and sometimes hydrotetrazones. When a phenylhydrazone of an aldehyde is oxidized with mercuric oxide, amyl nitrite, or iodine,[2] three products are obtained which seem to be formed from radicals derived from the hydrazone. The phenylhydrazone of benzaldehyde gives a dibenzaldiphenyltetrazane (I), a derivative of benzhydrazidine, usually called dehydrobenzalphenylhydrazone (II), and the osazone (di-phenylhydrazone) of benzil (III). The first may arise from the polymerization of two nitrogen radicals, the second from that of a nitrogen and a carbon radical, and the third from two carbon radicals.

$$\phi \cdot CH:N \cdot \underset{\cdot}{N}\phi \;\longleftarrow\; \phi \cdot CH:N \cdot NH\phi \;\longrightarrow\; \phi \cdot \underset{\cdot}{C}:N \cdot NH\phi$$

$$
\begin{array}{ccc}
\phi \cdot CH:N \cdot N\phi & \phi \cdot C:N \cdot NH\phi & \phi \cdot C:N \cdot NH\phi \\
\;\;\;\;\; | & \;\;\;\;\; | & \;\;\;\;\; | \\
\phi \cdot CH:N \cdot N\phi & \phi \cdot N \cdot N:CH\phi & \phi \cdot C:N \cdot NH\phi \\
\text{I.} & \text{II.} & \text{III.}
\end{array}
$$

Dibenzaldiphenyltetrazane (I) melts with decomposition at 187°, and is sparingly soluble in all solvents. It undergoes interesting rearrangements which may possibly result from its dissociation into free radicals. If heated slowly it is transformed into the benzhydrazidine derivative (II), and in the presence of alcoholic potash or alcoholic hydrogen chloride the re-arrangement proceeds further to the osazone (III).[3] It dissolves in strong sulphuric acid with a deep blue colour, and this is most probably the origin of Bülow's test for phenylhydrazones, the brilliant colour which they give when treated in sulphuric acid with a little ferric chloride or potassium dichromate.

Tetrazanes which contain an acyl group are formed in small quantity when the phenylhydrazones of certain aldehydes are slowly oxidized by passing oxygen through their alcoholic solutions. Benzaldehyde phenyl-hydrazone, for example, gives benzoylbenzaldiphenyltetrazane,

$$\phi CO \cdot NH \cdot N\phi \cdot N\phi \cdot N:CH\phi.$$

[1] The effect of substituents on the extent of dissociation is discussed by C. K. Ingold, *Trans. Faraday Soc.* 1934, **30**, 52.

[2] H. v. Pechmann, *Ber.* 1893, **26**, 1045; G. Minunni, *Gazz.* 1892, **22** [2], 228.

[3] H. Ingle and H. H. Mann, *J.C.S.* 1895, **67**, 607.

Their formation is due to oxidation of some of the hydrazone to benzoyl-azobenzene.[1]

$$\phi CH:N \cdot NH\phi \longrightarrow \phi CO \cdot N:N \cdot \phi$$

This compound then condenses with unchanged hydrazone.

$$\begin{array}{c} \phi CH:N \cdot NH\phi \\ + \\ \phi CO \cdot N:N \cdot \phi \end{array} \longrightarrow \begin{array}{c} \phi CH:N \cdot N\phi \\ | \\ \phi CO \cdot NH \cdot N\phi \end{array}$$

This view is supported by the fact that benzoylazobenzene, which can be obtained by the oxidation of benzoyl-phenylhydrazine, $\phi CO \cdot NH \cdot NH\phi$, condenses rapidly with benzaldehyde phenylhydrazone at room temperature in ether in presence of a little acetic acid. The constitution of the compound is shown by the products obtained on reduction. When treated with glacial acetic acid and zinc dust, it gives nothing but benzaldehyde phenylhydrazone and benzoyl-phenylhydrazine, the molecule being split between the two central nitrogen atoms. These tetrazanes are unstable compounds, and on standing undergo a complicated series of rearrangements.

Tetrazenes contain an unsaturated chain of four nitrogen atoms. The symmetrical derivatives with the double bond in the middle of the chain are prepared by the oxidation of the unsymmetrically di-substituted hydrazines:

$$2RR'N \cdot NH_2 \longrightarrow RR'N \cdot N:N \cdot NRR'.$$

The best oxidizing agent is azodicarboxylic ester which takes up the hydrogen atoms and is reduced to the hydrazo ester,[2]

$$EtO_2C \cdot NH \cdot NH \cdot CO_2Et.$$

Mercuric oxide, ferric chloride, and hypochlorous acid have also been used, and the reaction is general for all unsymmetrically di-substituted hydrazines. These tetrazenes are pale yellow oils or low-melting solids. Some of them can be distilled under reduced pressure, but they all lose nitrogen at about 120–140° and are converted into tetra-substituted hydrazines, a behaviour which is shared by other compounds containing doubly bound nitrogen atoms (see p. 432).

$$R_2N \cdot N:N \cdot NR_2 \longrightarrow R_2N \cdot NR_2 + N_2$$

When they are treated with acids, they form unstable salts which resemble those of the tetra-substituted hydrazines (see p. 391), and if the solution is warmed, nitrogen is lost and the decomposition products of the hydrazine formed.[3]

Reduction of tetraphenyl tetrazene, either catalytically with palladium or with zinc and acid, gives nothing but diphenylamine. The tetrazane first formed immediately loses nitrogen.[4]

$$\phi_2N \cdot N:N \cdot N\phi_2 \longrightarrow \phi_2N \cdot NH \cdot NH \cdot N\phi_2 \longrightarrow 2\phi_2NH + N_2$$

[1] M. Busch and H. Kunder, *Ber.* 1916, **49**, 2347.
[2] O. Diels, ibid. 1923, **56**, 1932. [3] H. Wieland, ibid. 1908, **41**, 3498.
[4] C. Paal and W. N. Yao, ibid. 1930, **63**, 57.

The derivatives of the unsymmetrical tetrazene, $HN:N \cdot NH \cdot NH_2$, are formed when an aromatic diazo compound is coupled with a substituted hydrazine in neutral solution, and in the oxidation of such a hydrazine by iodine.[1] Because of the first method of preparation they are called diazo-hydrazides. The product from diazobenzene and phenylhydrazine has the constitution $\phi \cdot N:N \cdot N\phi \cdot NH_2$, and not $\phi \cdot N:N \cdot NH \cdot NH\phi$; i.e. coupling takes place on to the secondary, and not the primary amino group of the hydrazine. This is shown by the fact that the compounds condense with aldehydes, which indicates the presence of an $—NH_2$ group.[2] Further the 1,4-diphenyl compound would be tautomeric with the derivatives of symmetrical tetrazene which have been discussed, and there is no inter-conversion of the two known types of tetrazenes:

$$\phi \cdot N:N \cdot NH \cdot NH\phi; \qquad \phi \cdot NH \cdot N:N \cdot NH\phi.$$

These tetrazenes are unstable oils or low-melting solids, and are often explosive. They are decomposed on warming or on treatment with acids and appear to break down rather like a diazoamino compound into a hydrazine and a diazo compound, or the further decomposition products of these:

$$R \cdot N:N \cdot NR' \cdot NH_2 \xrightarrow{\text{HCl}} RN_2Cl + R'NH \cdot NH_2.$$

Pentazane Derivatives

The only compounds known to contain a chain of five nitrogen atoms are the bis-diazoamino compounds, $Ar \cdot N:N \cdot NR \cdot N:N \cdot Ar$. They are formed very readily from primary aliphatic amines (and ammonia) by coupling with aromatic diazo compounds.[3]

$$2\phi \cdot N_2Cl + H_2NMe \longrightarrow \phi \cdot N:N \cdot NMe \cdot N:N \cdot \phi$$

With aromatic primary amines the reaction usually stops at the diazo-amino stage, but in alkaline solution the bis-compound can sometimes be obtained. The reaction is no doubt a two-stage process, the diazoamino compound being the intermediate product. If this is so, the compound obtained from diazobenzene and methylamine might have an unsym-metrical formula,

$$\phi \cdot N_2Cl + \phi \cdot NH \cdot N:N \cdot Me \longrightarrow \phi \cdot N:N \cdot N\phi \cdot N:N \cdot Me.$$

However, the product of coupling diazobenzene and tolylmethyltriazene, $C_7H_7 \cdot NH \cdot N:NMe$, is identical with that obtained from diazotoluene and phenylmethyltriazene,[4] so the symmetrical formula shown, with the alkyl group on the central nitrogen atom, is probably correct.

The bis-diazoamino compounds are crystalline solids which resemble

[1] A. Wohl and H. Schiff, *Ber.* 1900, **33**, 2741; R. Stollé, *J. pr. Chem.* 1902, **66**, 337.
[2] M. Busch and H. Pfeiffer, *Ber.* 1926, **59**, 1162.
[3] H. v. Pechmann and L. Frobenius, ibid. 1894, **27**, 705.
[4] O. Dimroth, M. Eble, and W. Gruhl, ibid. 1907, **40**, 2390.

the diazoamino compounds but are more explosive: some of them can be detonated by a blow. When treated with hydrogen chloride in an inert solvent, they are decomposed to one molecule of a diazonium chloride and one of a triazene which further decomposes with loss of nitrogen:

$$\phi \cdot N:N \cdot NMe \cdot N:N \cdot \phi \longrightarrow \phi \cdot N_2Cl + NHMe \cdot N:N \cdot \phi.$$

With aqueous acids the final products are nitrogen, phenol, aniline, methylamine, and methyl alcohol.

Octazane Derivatives

The longest nitrogen chain known consists of eight nitrogen atoms with three double bonds, and is present in the substances known as octazones and more correctly described as octaztrienes. These compounds are very unstable and explosive and decompose rapidly under all conditions. To use Wieland's phrase, they stand on the edge of existence. They are prepared by the oxidation of the diazohydrazides (see above) by stirring the ethereal solution with dilute aqueous permanganate at $0°$.[1] The reaction is similar to the preparation of a tetrazene from a di-substituted hydrazine.

$$2\phi \cdot N:N \cdot N\phi \cdot NH_2 \longrightarrow \phi N:N \cdot N\phi \cdot N:N \cdot N\phi \cdot N:N \cdot \phi$$

They are low-melting yellow solids which are difficult to purify because of their great instability.

[1] A. Wohl and H. Schiff, ibid. 1900, **33**, 2741.

CHAPTER XVI

CYCLIC POLYMETHYLENE-IMINES (EXCLUDING PYRROLIDINE AND PIPERIDINE)

THE cyclic polymethylene-imines are compounds which contain a saturated ring made up of a certain number of carbon atoms and one nitrogen atom. Thus we have ethylene-imine (I), and propylene-imine (II).

$$\text{I.} \quad \begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix} \bigg\rangle NH \qquad\qquad \text{II.} \quad \begin{matrix} CH_2-CH_2 \\ | \qquad | \\ CH_2-NH \end{matrix}$$

The five- and six-membered rings are called pyrrolidine and piperidine, respectively. Because of the number of atoms in their rings these two compounds differ from the remainder of the class. There is no strain in the rings and thus they are more stable than the three- and four-membered rings; they are much easier to prepare from open chain compounds than the compounds with a larger number of atoms in the ring, because there is a much greater probability of approach of the two ends of a five- or six-membered chain. The five- and six-membered rings are also closely related to the aromatic substances pyrrole and pyridine, respectively; hence they are discussed in the two following chapters of this book.

The polymethylene-imines have been synthesized in two ways, (1) by heating the dihydrochlorides of the polymethylenediamines, and (2) by treating the ω-halogen-amines with alkalis:

$$(1) \quad HCl,NH_2(CH_2)_nNH_2,HCl \longrightarrow NH_4Cl + (CH_2)_nNH,HCl$$

$$(2) \quad Br(CH_2)_nNH_2 + NaOH \longrightarrow NaBr + H_2O + (CH_2)_nNH.$$

Method (1) is of very limited application. Although the dihydrochlorides of tetra- and pentamethylene diamine are converted smoothly into tetramethylene-imine (pyrrolidine) and pentamethylene-imine (piperidine), respectively, ethylene diamine dihydrochloride ($n = 2$) when heated yields the six-membered ring piperazine,[1] $NH(CH_2 \cdot CH_2)_2NH$; and trimethylene diamine dihydrochloride gives only a very poor yield of the four-membered trimethylene-imine. It seems impossible to prepare rings larger than six-membered by this method, and, indeed, the statement is frequently to be found in text-books that octamethylene diamine dihydrochloride yields α-n-butylpyrrolidine on heating.[2] α-n-Butylpyrrolidine has, however, been synthesized by two independent methods,[3] and its properties differ widely from those ascribed to the substance produced by the distillation of octamethylene diamine dihydrochloride.

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[1] A. Ladenburg and J. Abel, *Ber.* 1888, **21**, 758; A. W. v. Hofmann, ibid. 1890, **23**, 3297.　　　　　[2] E. E. Blaise and L. Houillon, *C.r.* 1906, **142**, 1541.

[3] K. Hess, *Ber.* 1919, **52**, 1636.

Method (2) is of considerably wider application. β-Bromo-ethylamine when treated with silver oxide or potassium hydroxide yields ethylene-imine,

$$\begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!\Big\rangle NH,[1]$$

as a colourless ammoniacal smelling liquid, boiling-point 55°. As in ethylene oxide the ring is readily opened; thus hydrobromic acid in the cold converts it into β-bromo-ethylamine, and with aqueous sulphur dioxide it reacts to give taurine, $HO_3S \cdot CH_2 \cdot CH_2 \cdot NH_2$. The facts that it is stable towards potassium permanganate and bromine, and reacts with benzenesulphonyl chloride to yield an alkali-insoluble sulphonamide, show that the substance is a secondary base and that it is not vinylamine, $CH_2:CH \cdot NH_2$, as was at one time supposed.[2] Ethylene-imine can be prepared in good yield from mono-ethanolamine, $HO \cdot CH_2 \cdot CH_2 \cdot NH_2$, which is a commercial product obtained from ethylene oxide and ammonia.[3] The hydroxy-amine is heated with sulphuric acid, when the hydroxyl group is esterified; the product is an internal salt.

$$NH_2 \cdot CH_2 \cdot CH_2 \cdot OH \longrightarrow \overset{+}{N}H_3 \cdot CH_2 \cdot CH_2 \cdot O \cdot SO_2 \cdot O^-$$

Distillation of this product with aqueous caustic soda gives ethylene-imine.

$$\begin{matrix} CH_2 \cdot O \cdot SO_2 \cdot O^- \\ | \\ CH_2 \cdot NH_3^+ \end{matrix} \longrightarrow \begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!\Big\rangle NH + H_2SO_4$$

Of the substituted ethylene-imines, the best known are the monophenyl and diphenyl derivatives. The former, $\phi CH\text{——}CH_2$, is a somewhat unstable oil, soluble in water, which readily polymerizes, especially in the presence of alkali.[4] It is strongly basic, but its hydrochloride reverts very readily to β-phenyl-β-chloro-ethylamine, $\phi \cdot CHCl \cdot CH_2NH_2$, from which it is obtained by the action of alkali. The $\alpha\beta$-diphenyl compound, $\phi CH\text{——}CH\phi$, exists in two geometrically isomeric forms, in one of which the two phenyl groups are on the same side of the ring and in the other on opposite sides. The two isomers can be obtained from the two optically isomeric forms of α-amino-β-chlorodibenzyl, a compound which contains two different asymmetric carbon atoms and hence exists in two isomeric forms. Of the two diphenylethylene-imines, the *trans* compound should be capable of displaying optical activity, while the molecule of the *cis* compound has a plane of symmetry and should be always inactive. This prediction has been verified:[5] if *laevo* iso-amino-chlorodibenzyl is treated with a solution of potash in alcohol, a laevorotatory diphenylethylene-imine (melting-point

S. Gabriel, ibid. 1888, **21**, 1049; S. Gabriel and R. Stelzner, ibid. 1895, **28**, 2929.

C. C. Howard and W. Marckwald, ibid. 1899, **32**, 2036.

H. Wenker, *J. Amer. C. S.* 1935, **57**, 2328.

F. Wolfheim, *Ber.* 1914, **47**, 1450.

A. Weissberger and H. Bach, ibid. 1931, **64**, 1095.

62–63°) is obtained: if, however, the starting material is the isomeric *laevo* amino-chlorodibenzyl, an inactive diphenylethylene-imine (melting-point 82–83°) is the product. The latter is clearly the *cis* compound (II) and the former the *trans* (I).

I.   II.

The occurrence of an optically active diphenylethylene-imine is the clearest proof that the molecule contains a ring structure. The alternative vinylamine structure, $\phi CH : C\phi \cdot NH_2$, could give rise to two geometrical isomers, but neither of these could be optically active.

The opening of an ethylene-imine ring to an open chain molecule, as for example, by the action of hydrogen halide, presents several points of interest. In the case of the diphenyl derivatives and hydrogen chloride two products are possible—the two optically isomeric amino-chlorodibenzyls: it has been found[1] that both *cis* and *trans* compounds give a mixture of the two dibenzyls. This must mean that in this case both *cis* and *trans* addition take place when the ring opens, in contrast to the hydrolytic opening of an ethylene oxide ring where only *trans* addition takes place.[2] If a β-chloro- or bromo-ethylamine is placed in neutral solution, it is partially converted into the hydrochloride or hydrobromide of the corresponding ethylene-imine, and an equilibrium is set up between the two, although side reactions also occur to some extent.[3]

$$R \cdot CHCl \cdot CH_2 \cdot NH_2 \; \rightleftharpoons \; \begin{matrix} RCH \!-\! CH_2 \\ \diagdown \; \diagup \\ NH, HCl \end{matrix}$$

If now blood charcoal is added to the solution, the equilibrium is displaced in favour of the chloro-amine, and correspondingly it can be shown that the rate of formation of ethylene-imine is slower in the presence of the charcoal, while that of the formation of chloro-amine from the ethylene-imine is accelerated.[4] This effect on the position of equilibrium arises from the fact that the chloro-amine is more strongly adsorbed on the charcoal than the imine hydrochloride; for, on simple thermodynamic grounds, the equilibrium will shift in favour of the more strongly adsorbed substance. The mechanism whereby the rate of ring closure is smaller when the chloro-amine is adsorbed on the charcoal seems to be that the orientation of the molecule is such that the probability of the necessary close approach of the halogen atom and the amino group is less than in homogeneous solution.

[1] A. Weissberger and H. Bach, *Ber.* 1932, **65**, 631.

[2] R. Kuhn and F. Ebel, ibid. 1925, **58**, 919.

[3] H. Freundlich and H. Kroepelin, *Z. phys. Chem.* 1926, **122**, 39.

[4] H. Freundlich and F. Juliusberger, ibid. 1930, A, **146**, 321; Freundlich and G. Salomon, ibid. 1933, A, **166**, 179.

N-phenyl substituted ethylene-imines can be prepared in many cases by a reaction discovered by L. Wolff.[1] Phenyl azide will condense with certain ethylenic compounds to give dihydro-1,2,3-triazoles (I): in some cases, especially when the double bond is in a six-membered ring with a 1,4-bridge methylene group (II), this reaction takes place with great ease at room temperature;[2] with compounds such as styrene ($\phi \cdot CH=CH_2$) and fumaric ester the addition takes place slowly if the reaction mixture is heated to 100° (see p. 373).

I.   II.

The dihydrotriazoles decompose on heating above their melting-points with loss of nitrogen[3] and formation either of an ethylene-imine (III) or of an anil (IV), or of a mixture of these two.

The two modes of decomposition are almost certainly the two possible rearrangements of the free radical (V), and recall the two types of products formed in the action of diazomethane on a ketone (see p. 359). With simple aliphatic olefines the product is almost entirely the anil (IV); styrene gives a mixture of anil and ethylene-imine and the bicyclic olefines such as (II) give nothing but the ethylene-imine. These N-phenyl ethylene-imines resemble the unsubstituted compounds in that with aqueous acids the three-membered ring is opened and an α-amino-alcohol formed.

The four-membered trimethylene-imine, $(CH_2)_3NH$, boiling-point 63°, is best prepared by a modification of method (2). Trimethylene dibromide reacts with p-toluenesulphonamide and alkali to give the p-toluene-sulphonyl derivative of trimethylene-imine, $CH_3 \cdot C_6H_4 \cdot SO_2N(CH_2)_3$. Trimethylene-imine cannot be prepared by acid hydrolysis of this imide, since mineral acids readily cause the opening of the cyclic imine; the p-toluene-sulphonyl group can be removed by the action of sodium in amyl alcohol,

[1] *Annalen*, 1912, **394**, 68.   [2] K. Alder and G. Stein, ibid, 1931, **485**, 211.
[3] Ibid. 1933, **501**, 9.

when trimethylene-imine, toluene and sulphurous acid are formed. Tri-methylene-imine reacts with hydrochloric acid to give γ-chloropropyl-amine, $CH_2Cl \cdot CH_2 \cdot CH_2 \cdot NH_2$; with sulphuric acid it gives γ-hydroxy-propylamine, $CH_2OH \cdot CH_2 \cdot CH_2 \cdot NH_2$, and with nitrous acid an N-nitroso derivative.

Although pyrrolidine and piperidine are readily prepared by method (2), it does not give good yields of the higher members. Thus von Braun[1] obtained only very poor yields of hexamethylene-imine by this method, and A. Müller and P. Krauss[2] could get no more than a 5 per cent. yield of the same product; heptamethylene-imine could not be obtained by this method. The reaction has, however, been successfully applied to the synthesis of large-ring imines by L. Ruzicka, G. Salomon, and K. E. Meyer[3] by taking advantage of a method first devised by K. Ziegler.[4] This is, briefly, that reaction between two active groups at opposite ends of a long hydrocarbon chain to form a ring compound is more likely to occur as the sole reaction in exceedingly dilute solution than in solutions of ordinary concentration; this is because the chances of intramolecular reaction are unaffected by dilution, whilst the chances of intermolecular reaction are thereby diminished, and, if the solution be sufficiently dilute, will be almost completely excluded. They heated the hydrobromide of ω-bromohexylamine in 0·01 molar solution with dilute sodium hydroxide, and obtained a 50 per cent. yield of hexamethylene-imine, and applying the same reaction to ω-bromohexadecylamine hydrochloride in butyl alcoholic solution at 120° obtained cyclohexadecylimine, $(CH_2)_{16}NH$, in over 50 per cent. yield. This large-ring imine possesses the same musk odour which is characteristic of the cyclic ketones, lactones, anhydrides, and esters containing between 14 and 19 carbon atoms. K. Ziegler and P. Orth[5] had previously obtained hexamethylene-imine as its p-toluene-sulphonyl derivative in 70 per cent. yield by treating the p-toluene-sulphonyl derivative of ω-bromo-n-hexylamine with sodium butylate in dilute butyl alcohol.

$$CH_3 \cdot C_6H_4 \cdot SO_2 \cdot NH \cdot (CH_2)_6Br \longrightarrow CH_3 \cdot C_6H_4 \cdot SO_2 \cdot N(CH_2)_6 + HBr$$

Large cyclic imines have also been prepared from the large-ring ketones by a series of reactions which converts a cyclic ketone of the formula $(CH_2)_nCO$ into a cyclic imine of the formula $(CH_2)_{n+1}NH$.[6] The ketone is converted into its oxime, which by the action of sulphuric acid undergoes the Beckmann rearrangement into the cyclic amide containing one more member in the ring; the amide is then converted into the thio-amide by treatment with potassium sulphide and phosphorous pentasulphide and

[1] J. v. Braun, et al., Ber. 1905, **38**, 3083; 1910, **43**, 2853; 1913, **46**, 1788; 1927, **60**, 1533.

[2] Monats. 1932, **61**, 219.   [3] Helv. Chim. Acta, 1934, **17**, 882.

[4] K. Ziegler, H. Eberle, and H. Ohlinger, Annalen, 1933, **504**, 94.

[5] Ber. 1933, **66**, 1867.

[6] L. Ruzicka, M. W. Goldberg, M. Hürbin, and H. A. Bockenoogen, Helv. Chim. Acta, 1933, **16**, 1323.

subsequently reduced to the cyclic imine, either electrolytically or by the action of sodium in ethyl alcohol-acetic acid.

$$(CH_2)_{13}\Big\langle {}^{C:NOH}_{CH_2} \longrightarrow (CH_2)_{14}\Big\langle {}^{CO}_{NH} \longrightarrow (CH_2)_{14}\Big\langle {}^{CS}_{NH} \longrightarrow (CH_2)_{15}NH$$

The smooth change from the fifteen-membered cyclic oxime to the sixteen-membered cyclic amide is of considerable interest, since it proves that during the Beckmann transformation the ring at no time passes through an open chain phase. If it did so, the ring would not close again except possibly to an exceedingly minute extent.

These cyclic polymethylene-imines with seven or more members in the ring are perfectly stable substances, and, as in the case of pyrrolidine and piperidine, there is no tendency for the ring to open under the influence of halogen acids, ammonia, &c. It is apparent that the strain in the planar three- and four-membered rings is absent in these higher members, and like the higher members of the cyclo-paraffin series, they must possess buckled rings. In their chemical behaviour they exactly resemble the secondary aliphatic amines.

CHAPTER XVII

FIVE-MEMBERED RINGS

A GREAT variety of five-membered ring systems containing nitrogen has been investigated. Of these only one class will be dealt with here, that in which the ring consists of four carbon atoms and one nitrogen atom. This class includes the pyrrole and indole groups and their reduction products.

PYRROLE GROUP[1]

The pyrrole group is important from many points of view. Members of the group are widely distributed in nature; of the reduced pyrrole derivatives proline (pyrrolidine-2-carboxylic acid) is a product of hydrolysis of nearly all proteins, and stachydrine and hygrine are simple pyrrolidine alkaloids; nicotine contains a pyrrolidine ring joined to a pyridine ring, atropine and cocaine contain pyrrolidine and piperidine rings fused together, and cuskhygrine is a derivative of dipyrrolidyl propane. More important are the tetrapyrrole compounds, comprising the porphyrins, of which haemoglobin and chlorophyll are derivatives, and another type of tetrapyrrole compound is found in the bile pigments and in certain pigments of algae. Our knowledge of the tetrapyrrole group is mainly owed to the analytical and synthetical experiments of Hans Fischer. No attempt is made here to deal with the chemistry of the porphyrins themselves, or of their more complex degradation products.[2]

Pyrrole was discovered by F. F. Runge in 1834 in coal-tar, but was first isolated in a pure condition by T. Anderson in 1858,[3] who obtained it from the products of distillation of bone, the so-called bone oil. This is still the chief source of pyrrole and certain homologues. The bone-oil is freed from its strongly basic constituents, mainly the pyridine compounds (pyrrole and its homologues are very weak bases), and then contains nitriles of the fatty acids, benzene hydrocarbons, pyrrole, and its homologues. The nitriles are removed by saponification with potash, and the liquid fractionated. The pyrrole is contained in the fraction boiling at 115–130°, and is isolated by conversion into its solid potassium derivative, from which the pyrrole is regenerated by steam-distillation. The name pyrrole is derived from πυρρός, fiery red, because a pine shaving moistened with hydro-

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[1] A valuable monograph is by H. Fischer and H. Orth, *Die Chemie des Pyrroles*, vol. i, Leipzig, 1934.

[2] Reference may be made to the article on 'The Chemistry of Chlorophyll', by K. F. Armstrong, *Chem. and Ind.* 1933, **11**, 809; to Richter-Anschütz, *Chemie der Kohlenstoffverbindungen*, 1931, iii. 35; to A. Kirrmann, *Bull. Soc. chim.* 1930, **47**, 913; to H. Fischer and Orth, op. cit. vol. ii, to be published; and to R. P. Linstead, *Ann. Reports Chem. Soc.* 1935, **32**, 359.

[3] *Trans. Roy. Soc. Edin.* **16**, 123, 463.

chloric acid develops a red colour when exposed to its vapour. This reaction is also shown by many derivatives of pyrrole, and a few other compounds.

Pyrrole is a colourless liquid, boiling-point 131°, with a characteristic odour recalling that of chloroform; it turns brown on exposure to the air. It is miscible with most organic liquids, but is only slightly soluble in water. Its molecular formula is C_4H_5N, and the constitution shown below was first advanced in 1870 by A. Baeyer, and, with some modification of the distribution of the valency electrons, this structure is universally accepted.

$$\text{I.}\quad \begin{array}{c} \overset{4}{C}H\!-\!-\!\overset{3}{C}H\beta \\ \| \qquad \| \\ \overset{5}{C}H \quad \overset{2}{C}H\alpha \\ \diagdown\underset{1}{N}\diagup \\ H \end{array} \qquad \text{II.}\quad \begin{array}{c} \boxed{} \\ NH \end{array}$$

The ring is numbered as shown (I); pyrroles substituted on the nitrogen atom are frequently described as N-derivatives, and with substituents on the carbon atoms as α- and β-derivatives. The unsubstituted pyrrole nucleus is usually written as in (II).

Syntheses of Pyrroles. Pyrrole has been synthesized by distilling the ammonium salt of mucic or saccharic acid ;[1] the yield is much improved by using glycerine as solvent in the presence of ammonia,[2] when about 40 per cent. of the theoretical amount can be obtained.[3]

$$\begin{array}{l} \text{CHOH·CHOH·CO}_2\text{NH}_4 \\ | \\ \text{CHOH·CHOH·CO}_2\text{NH}_4 \end{array} \longrightarrow \begin{array}{l} \text{CH=CH} \\ | \qquad\quad \diagdown \text{NH} + 2\text{CO}_2 + \text{NH}_3 + 4\text{H}_2\text{O} \\ \text{CH=CH} \diagup \end{array}$$

Pyrrole is produced in small quantity by the passage of acetylene and ammonia through a red-hot tube,

$$2\text{C}_2\text{H}_2 + \text{NH}_3 \longrightarrow \text{C}_4\text{H}_5\text{N} + \text{H}_2$$

and by the reduction of succinimide by heating with zinc dust or metallic sodium.

$$\begin{array}{l} \text{CH}_2\!-\!\text{CO} \\ | \qquad\quad \diagdown \text{NH} \\ \text{CH}_2\!-\!\text{CO} \diagup \end{array} \longrightarrow \begin{array}{l} \text{CH=CH} \\ | \qquad\quad \diagdown \text{NH} \\ \text{CH=CH} \diagup \end{array}$$

Succinimide and dichloromaleic imide give perchlorinated pyrroles when they are heated with phosphorus pentachloride; these compounds have a structure derived from the pyrrolenine form of the pyrrole nucleus. They can be reduced to tetrachloropyrrole, which is converted into tetra-iodopyrrole by potassium iodide. The latter is reduced by zinc dust in alkaline solution to pyrrole itself.

[1] H. Schwanert, *Annalen*, 1860, **116**, 278.
[2] M. Goldschmidt, *Z. f. Chem.* 1867, **3**, 280.
[3] E. Khotinsky, *Ber.* 1909, **42**, 2506.

$$
\begin{array}{ccc}
\text{CCl—CO} & \text{CCl—CCl} & \\
\| \qquad \rangle\text{NH} & \| \quad \| \quad \rangle\text{N} & \text{CCl}\!=\!\text{CCl} \\
\text{CCl—CO} & \text{CCl—CCl}_2 & \text{CCl}\!=\!\text{CCl}\rangle\text{NH} \longrightarrow \text{CH}\!=\!\text{CH}\rangle\text{NH} \\
& \text{CCl}_2\!-\!\text{CCl} & \text{CCl}\!=\!\text{CCl} \qquad \text{CH}\!=\!\text{CH} \\
& \| \quad \| \quad \rangle\text{N} & \\
& \text{CCl}_2\!-\!\text{CCl}_2 &
\end{array}
$$

The foregoing syntheses are of little practical importance, and cannot be applied to the preparation of substituted pyrroles. A method of considerable general interest is the preparation of pyrroles from γ-diketones, e.g. acetonylacetone, by the action of ammonia (L. Knorr). Acetonylacetone, itself prepared from sodioacetoacetic ester by the action of iodine and hydrolysis of the resulting diacetylsuccinic ester with cold aqueous sodium hydroxide, reacts with ammonia to give 2,5-dimethylpyrrole, the reaction being conveniently regarded as taking place through the dienolic form.

$$
\begin{array}{ccc}
\text{CH}_2\!-\!\text{CO} & \text{CH}\!=\!\text{C} & \text{CH}\!=\!\text{C} \\
| \qquad \rangle\text{CH}_3 & | \quad \langle^{\text{CH}_3}_{\text{OH}} & | \quad \langle^{\text{CH}_3}_{} \\
\text{CH}_2\!-\!\text{CO} & \text{CH}\!=\!\text{C} & \text{CH}\!=\!\text{C} \\
\qquad \rangle\text{CH}_3 & \langle^{\text{OH}}_{\text{CH}_3} & \rangle\text{NH} \quad \langle^{}_{\text{CH}_3}
\end{array}
$$

It may be recalled that the action of dehydrating agents on acetonylacetone gives 2,5-dimethylfurane, and the action of phosphorous pentasulphide gives 2,5-dimethylthiophene. This method of preparation of pyrroles has been investigated in some detail by L. Knorr and P. Rabe,[1] who have isolated an intermediate stage in the reaction between ammonia and diacetylsuccinic ester by working in ethereal solution at 0°.

$$
\begin{array}{ccc}
\text{EtO}_2\text{C}\!\cdot\!\text{CH}\!-\!\text{CO} & \text{EtO}_2\text{C}\!\cdot\!\text{C}\!=\!\text{C} & \text{EtO}_2\text{C}\!\cdot\!\text{C}\!=\!\text{C} \\
| \qquad \rangle\text{CH}_3 & | \quad \langle^{\text{CH}_3}_{\text{OH}} & | \quad \langle^{\text{CH}_3}_{} \\
\text{EtO}_2\text{C}\!\cdot\!\text{CH}\!-\!\text{CO} & \text{EtO}_2\text{C}\!\cdot\!\text{C}\!=\!\text{C} & \text{EtO}_2\text{C}\!\cdot\!\text{C}\!=\!\text{C} \\
\qquad \rangle\text{CH}_3 & \langle^{\text{NH}_2}_{\text{CH}_3} & \rangle\text{NH} \quad \langle^{}_{\text{CH}_3}
\end{array}
$$

At ordinary temperatures the substituted pyrrole is produced. The reaction is capable of extension to any γ-diketone or γ-diketonic ester, and the ammonia may be replaced by any primary aliphatic or aromatic amine, hydrazine or hydroxylamine.

Another and more valuable synthesis of pyrroles is also due to Knorr.[2] This consists essentially in the condensation of a ketone with an α-aminoketone in the presence of an alkali. The reaction is conveniently carried out by reducing the oximino-ketone (usually readily prepared from the ketone by treatment with an ester of nitrous acid) to the amino-ketone with zinc dust in acetic acid solution; then, without isolating the amino-

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[1] *Ber.* 1900, **33**, 3801.   [2] Ibid. 1884, **17**, 1635; *Annalen*, 1885, **236**, 290.

ketone, the ketone is added and the mixture made alkaline. In the simple case of acetone and oximino-acetone the reaction can be represented as follows:

$$
\begin{array}{c}
\mathrm{CH_3\!-\!CO} \\
| \\
\mathrm{CH} \\
\parallel \\
\mathrm{NOH}
\end{array}
+
\begin{array}{c}
\mathrm{CH_3} \\
| \\
\mathrm{CO\!-\!CH_3}
\end{array}
\longrightarrow
\begin{array}{c}
\mathrm{CH_3\!-\!CO} \\
| \\
\mathrm{CH_2} \\
| \\
\mathrm{NH_2}
\end{array}
+
\begin{array}{c}
\mathrm{CH_3} \\
| \\
\mathrm{CO\!-\!CH_3}
\end{array}
$$

$$
\longrightarrow
\begin{array}{c}
\mathrm{CH_3\!-\!CO \quad CH_3} \\
| \qquad\quad | \\
\mathrm{CH_2 \quad\; C\!-\!CH_3} \\
\diagdown \quad \diagup \\
\mathrm{N}
\end{array}
\longrightarrow
\begin{array}{c}
\mathrm{CH_3\!-\!C\!-\!-\!CH} \\
| \qquad\quad | \\
\mathrm{CH \quad C\!-\!CH_3} \\
\diagdown \;/ \\
\mathrm{NH}
\end{array}
$$

This simplest form of the reaction is of but limited application and gives very poor yields, but the reaction is improved by substituting a β-diketone for the simple ketone.

$$
\begin{array}{c}
\mathrm{R'\!-\!CO} \\
| \\
\mathrm{R\!-\!CH} \\
| \\
\mathrm{NH_2}
\end{array}
+
\begin{array}{c}
\mathrm{H_2C\!-\!CO\!-\!R''} \\
| \\
\mathrm{CO\!-\!R'''}
\end{array}
\longrightarrow
\begin{array}{c}
\mathrm{R'\!-\!C\!-\!-\!C\!-\!CO\!-\!R''} \\
| \qquad\qquad | \\
\mathrm{R\!-\!C \qquad C\!-\!R'''} \\
\diagdown \quad\; \diagup \\
\mathrm{NH}
\end{array}
$$

If an oximino-β-ketonic ester is used, the yield is still better and often quantitative.

$$
\begin{array}{c}
\mathrm{R'\!-\!CO} \\
| \\
\mathrm{RO_2C\!-\!CH} \\
| \\
\mathrm{NH_2}
\end{array}
+
\begin{array}{c}
\mathrm{H_2C\!-\!CO\!-\!R''} \\
| \\
\mathrm{CO\!-\!R'''}
\end{array}
\longrightarrow
\begin{array}{c}
\mathrm{R'\!-\!C\!-\!-\!C\!-\!CO\!-\!R''} \\
| \qquad\qquad | \\
\mathrm{RO_2C\!-\!C \qquad C\!-\!R'''} \\
\diagdown \quad\;\; \diagup \\
\mathrm{NH}
\end{array}
$$

$$
\begin{array}{c}
\mathrm{R'\!-\!CO} \\
| \\
\mathrm{RO_2C\!-\!CH} \\
| \\
\mathrm{NH_2}
\end{array}
+
\begin{array}{c}
\mathrm{H_2C\!-\!CO_2R''} \\
| \\
\mathrm{CO\!-\!R'''}
\end{array}
\longrightarrow
\begin{array}{c}
\mathrm{R'\!-\!C\!-\!-\!C\!-\!CO_2R''} \\
| \qquad\qquad | \\
\mathrm{RO_2C\!-\!C \qquad C\!-\!R'''} \\
\diagdown \quad\;\; \diagup \\
\mathrm{NH}
\end{array}
$$

The various modifications of this second Knorr's synthesis have been used by H. Fischer in his syntheses of the various alkylated pyrroles and related compounds derived from the porphyrins. The synthesis can also be carried out by first isolating the amino-ketone and then condensing it with the β-keto-ester in alkaline solution.[1]

2,3,4,5-Tetraphenylpyrrole may be prepared by an interesting reaction from the azine of deoxybenzoin by the action of hydrogen chloride at 180°.[2] The reaction is exactly analogous to the indole synthesis of E. Fischer, and is the only case where this important reaction for the

[1] O. Piloty and P. Hirsch, ibid. 1913, 395, 63.
[2] R. Robinson and G. M. Robinson, J.C.S. 1918, 113, 639.

synthesis of indoles (see p. 498) has been applied to the synthesis of true pyrroles

$$
\begin{array}{cc}
\phi\cdot CH_2 & CH_2\cdot\phi \\
| & | \\
\phi\cdot C{=}N{-}N{=}C\cdot\phi
\end{array}
\longrightarrow
\begin{array}{cc}
\phi\cdot CH & CH\cdot\phi \\
\| & \| \\
\phi\cdot C{-}NH{-}NH{-}C\cdot\phi
\end{array}
$$

$$
\longrightarrow
\begin{array}{cc}
\phi\cdot C\text{---} & \text{---}C\cdot\phi \\
\| & \| \\
\phi\cdot C{-}NH_2 & NH_2{-}C\cdot\phi
\end{array}
\longrightarrow
\begin{array}{cc}
\phi\cdot C{-}C\cdot\phi \\
\| \quad \| \\
\phi\cdot C \quad C\cdot\phi \\
\diagdown \diagup \\
NH
\end{array}
$$

Chemical Properties of Pyrroles. The formula of pyrrole would suggest that it is a secondary base, but its basic properties are extremely weak. They are to some extent concealed by the fact that pyrrole, and most of its homologues, are very easily converted by acids into complicated red polymers, the so-called pyrrole-red, a conversion which is well known to all who have worked with pyrroles. Even in the few cases where polymerization does not occur, the salts are readily hydrolysed by water. Pyrrole itself dissolves slowly in cold dilute acids, pyrrole-red being produced on warming the solution; concentrated acids cause rapid resinification. Pyrrole will not combine with alkyl halides, but pyrroles in general form well-defined crystalline compounds with picric acid, styphnic acid (trinitro-resorcinol), and picrolonic acid (a dinitro derivative of the phenyl-methylpyrazolone formed from acetoacetic ester and phenylhydrazine); these are used for the isolation and identification of pyrroles.

Connected with the weak basicity of the NH group in pyrrole is the fact that this group shows definite acidic properties (compare the NH group in diphenylamine and carbazole). Metallic potassium readily dissolves in pyrrole with evolution of hydrogen to give potassium pyrrole, C_4H_4NK, and the same compound is produced by heating pyrrole with potassium hydroxide. Sodium reacts much less readily, and sodium hydroxide is almost without action upon pyrrole. Potassium pyrrole is a crystalline solid, decomposed by water into pyrrole and potassium hydroxide. It is the source of a large number of pyrrole derivatives, as on treatment with alkyl and acyl halides, chloroformic ester, &c., it gives the corresponding N-substituted pyrroles. These products are remarkable for the ease with which the substituent passes from the nitrogen to carbon on heating, as frequently happens with N-substituted anilines. For example:

$$
\begin{array}{c}
CH{=}CH \\
| \qquad\qquad >NK + C_2H_5I \\
CH{=}CH
\end{array}
\longrightarrow
\begin{array}{c}
CH{=}CH \\
| \qquad\qquad >NC_2H_5 \\
CH{=}CH
\end{array}
\longrightarrow
\begin{array}{c}
CH{=}C{<}^{C_2H_5} \\
| \qquad\qquad\quad >NH. \\
CH{=}CH
\end{array}
$$

The substituent usually migrates to the α-position, but the β-derivative is often simultaneously produced. The mechanism of these transformations is unknown.

In their general character, the pyrroles are definitely aromatic; they

possess the nuclear stability and diminished unsaturation of such compounds. Unlike thiophene, however, which resembles benzene to a remarkable degree, pyrrole resembles, not so much benzene, but phenol. This will be evident from the following account, as well as from the formation and properties of potassium pyrrole.

Halogens react energetically with pyrrole and, in order to prevent resinification, reactions must be carried out in dilute solution. The action of chlorine on pyrrole leads to the production of tetrachloropyrrole, melting-point 110°. Less highly substituted chloropyrroles have been prepared by the action of sulphuryl chloride in ethereal solution,[1] both α-positions being substituted before the β-positions are attacked; the ultimate product is pentachloropyrrole (III), which is derived from a pyrrolenine form of pyrrole (see p. 490).

$$\text{III.} \quad \begin{array}{c} \text{ClC—CCl} \\ \| \qquad \| \\ \text{ClC—CCl}_2 \end{array}\!\!>\!\!\text{N} \qquad\qquad \text{IV.} \quad \begin{array}{c} \text{Cl·C—CO} \\ \| \qquad \| \\ \text{Cl·C—CO} \end{array}\!\!>\!\!\text{NH}$$

Its constitution is established by the fact that on boiling with water, dichloromaleic imide (IV) is produced. Tetra-iodopyrrole, 'iodol', is prepared by the action of potassium iodide upon tetrachloropyrrole, or by the direct iodination of pyrrole in presence of alkali. It forms odourless, yellowish prisms, decomposing at 140–150°, and finds application as an antiseptic in place of iodoform. The action of alkali hypochlorites and hypobromites on pyrrole gives dichloro- and dibromo-maleic imide, respectively. Halogen atoms directly attached to the pyrrole nucleus are unreactive.

β-Nitrosopyrroles may be prepared in the form of their alkali salts by the action of amyl nitrite and sodium ethoxide on pyrroles; the free compounds are, for the most part, very unstable.

$$\begin{array}{c} \text{CH—CH} \\ \| \qquad \| \\ \text{CH} \quad \text{CH} \\ \diagdown\!\diagup \\ \text{NH} \end{array} + \text{C}_5\text{H}_{11}\!\cdot\!\text{ONO} + \text{NaOEt} \longrightarrow \begin{array}{c} \text{CH—C}\!\!=\!\!\text{N—ONa} \\ \| \qquad \| \\ \text{CH} \quad \text{CH} \\ \diagdown\!\text{N}\!\diagup \end{array} + \text{C}_5\text{H}_{11}\!\cdot\!\text{OH} + \text{HOEt}$$

These oximino compounds are derivatives of the tautomeric pyrrolenine form.

Nitration of pyrroles leads generally to complete decomposition, but a few polynitropyrroles have been made by the nitration of pyrrole carboxylic acids, halogenated pyrroles, &c. Formyl and acetyl groups attached to the α- or β-carbon atoms are readily replaced in alkyl pyrroles by NO_2 groups on treatment with concentrated nitric acid.[2] A more general method is to treat a pyrrole with ethyl nitrate and sodium ethoxide, when the nitro derivative separates as the explosive sodium derivative of the *aci*-form; this is subsequently decomposed by carbon dioxide in aqueous solution (see p. 8).

The *amino-pyrroles* are best prepared by the reduction of the nitroso or

[1] G. Mazzara and A. Borgo, *Gazz.* 1905, **35**, i. 477; ii. 100.

[2] H. Fischer and W. Zerweck, *Ber.* 1922, **55**, 1949.

nitro derivatives with aluminium amalgam in moist ether, or with sodium amalgam in alkaline solution. They are unstable compounds which show little resemblance to the amino derivatives of benzene. Pyrroles with phenyl substituents attached to the ring give more stable amino derivatives, but these cannot be diazotized like aromatic amines; the action of nitrous acid gives the so-called 'diazopyrroles', which are extremely stable and are unattacked by strong sulphuric acid. Their composition resembles that of the aliphatic diazo compounds, but their structure is not fully known.

Like phenol, pyrrole and its derivatives couple with the aromatic diazo compounds to give products in which the azo group is attached to a carbon atom of the pyrrole nucleus. Coupling takes place in both the α- and the β-positions, but more rapidly in the former. Pyrrole itself couples with benzene diazonium chloride in weakly acid solution to give a mono-azo, and in alkaline solution to give a dis-azo compound. Di-substituted pyrroles couple only once, while tetra-substituted pyrroles only couple if one of the substituents is a carboxyl group; this is eliminated in the reaction and replaced by the azo group. Reduction of the azo derivatives of pyrrole might be expected to give the amino-pyrroles, just as in the benzene series. Catalytic hydrogenation is, however, the only way in which the reaction can be carried out; with other reducing agents no amine can be obtained.[1]

Pyrroles which do not contain a substituent attached to the nitrogen atom react readily with Grignard compounds. The pyrrole behaves as a weak acid and sets free the hydrocarbon from the reagent, a pyrryl magnesium halide being formed. Thus with ethyl magnesium bromide, ethane is evolved.

$$\text{(ring)} + \text{EtMgBr} \longrightarrow \text{(ring)} + \text{EtH}$$
$$\qquad\text{NH} \qquad\qquad\qquad \text{NMgBr}$$

This fact can be used both for finding out whether or not a given pyrrole contains an N-substituent, and, by measuring the volume of ethane formed, for estimating pyrroles quantitatively.[2] The pyrryl magnesium halides are extremely valuable synthetic reagents, since they interact readily with a large variety of compounds giving not N-, but C-substituted pyrroles. There are two possibilities for their structure; either the magnesium may be attached to the nitrogen atom, as in (V), or else it may be attached to a carbon atom of the ring. Since in many of their reactions products containing a substituent in the α-position are formed, the view has been held that the magnesium first becomes attached to the nitrogen atom and then migrates to the α-carbon atom, as in (VI).[3]

---

[1] H. Fischer and F. Rothweiler, *Ber.* 1923, **56**, 512.

[2] See H. Meyer, *Analyse und Konstitutionsermittlung organ. Verbindungen*, 1931, p. 371; Houben-Weyl, *Die Methoden der organischen Chemie*, 1923, iii. 32.

[3] H. Fischer and H. Orth, op. cit., p. 122.

V.   VI.

Of these two alternatives the former is the more probable. The great majority of C-magnesium compounds show the phenomenon of chemiluminescence when they are exposed to gaseous oxygen, while N-magnesium compounds, such as those obtained by the action of an aromatic amine on a Grignard compound, do not. The pyrryl magnesium halides show no luminescence.[1] Further, if the migration to the C-compounds actually takes place, the products contain an —NH— group, and it is difficult to see why they do not then react with more ethyl magnesium bromide. The experimental fact is that even with large excess of the latter there is no further reaction after one hydrogen atom has been replaced by the magnesium residue.[2] Hence it would seem that in the pyrryl magnesium halides the magnesium is attached to the nitrogen atom, and the formation of C-substituted compounds in the reactions with other substances is a complicated matter whose mechanism is unknown.

Some typical reactions of the pyrryl magnesium halides are as follows; with water the pyrrole is regenerated; carbon dioxide and chloroformic ester give pyrrole α-carboxylic acids and esters respectively; acid chlorides give α-keto derivatives, and with formic ester pyrrole α-aldehydes are formed. The action of alkyl halides is more complicated; α-alkyl and αα'-dialkyl pyrroles are produced, but a certain amount of the β-alkyl compound is also formed.[3]

The pyrrole *aldehydes* are important synthetical reagents. Apart from the method of preparation through the pyrryl magnesium halides, pyrrole α-aldehyde itself is conveniently prepared by the Tiemann-Reimer reaction,[4] by the action of chloroform on an aqueous alcoholic solution of pyrrole in presence of potassium hydroxide.

An important method for preparing many substituted pyrrole aldehydes is Gattermann's synthesis; this gives good yields, and can be made to yield both α- and β-aldehydes.[5] The substituted pyrrole is dissolved in anhydrous ether or chloroform and treated with anhydrous hydrogen cyanide and hydrogen chloride. The aldimine hydrochloride

[1] C. M. McCay and C. L. A. Schmidt, *J. Amer. C. S.* 1926, **48**, 1933.

[2] H. Gilman and L. L. Heck, ibid. 1930, **52**, 4949.

[3] Further details will be found in the following monographs; B. Oddo, *Mem. R. Accad. Lincei*, 1923, (5), **14**, 510; F. Runge, *Organo-Metallverbindungen*, Stuttgart, 1932, vol. i, p. 217.

[4] E. Bamberger and G. Djierdjian, *Ber.* 1900, **33**, 536; H. Fischer, H. Beller, and A. Stern, ibid. 1928, **61**, 1078.

[5] H. Fischer and W. Zerweck, ibid. 1922, **55**, 1942.

separates in a crystalline condition, and is hydrolysed by warming with water.

The aldehyde group usually enters the α-position rather than the β-, and in order to obtain a pyrrole β-aldehyde with a free α-position the latter must be protected by the carbethoxy group, which is subsequently hydrolysed and eliminated as carbon dioxide. The pyrrole α-aldehydes have been largely used by H. Fischer in the synthesis of the coloured dipyrrylmethenes, isolated from blood pigments by acid hydrolysis,

and also for preparing methyl pyrroles by decomposition of their hydrazones by sodium methoxide (see p. 394). They show the usual chemical properties of the aromatic aldehydes; they are reduced to the corresponding carbinols by aluminium amalgam, and condense with malonic acid.

Ketones derived from pyrrole may be obtained by appropriate modifications of Knorr's synthetical processes, or by introduction of the acyl group into a preformed pyrrole. The latter process may be carried out (1) by the action of acid chlorides or esters on the pyrryl magnesium halides; (2) by the action of hydrogen chloride and an alkyl cyanide upon a dry ethereal solution of a pyrrole (application of the Hoesch synthesis of phenolic ketones), whereby both α- and β-pyrrole ketones may be prepared, as in the corresponding aldehyde synthesis; (3) by the Friedel-Crafts reaction: in presence of aluminium chloride acid chlorides condense with pyrroles in which either an α- or a β-position is free; the usual solvent is carbon disulphide; (4) by the action of an acid anhydride on a pyrrole at a high temperature: the N-acyl pyrrole is probably first formed and is transformed into an α-acyl pyrrole. The pyrryl ketones are quite stable compounds and many of them form salts with mineral acids without polymerization. They can be reduced to alkyl pyrroles by heating their hydrazones with sodium ethylate (see p. 394).

Pyrrole *carboxylic acids* may be prepared in great variety by the many synthetical processes available for the production of the pyrrole nucleus. The analogy between phenol and pyrrole is well brought out by the methods available for the introduction of the carboxyl group into pyrrole. These are (1) heating potassium pyrrole in a stream of carbon dioxide,

(2) heating pyrrole with ammonium carbonate under pressure, (3) the action of carbon tetrachloride and alcoholic alkali upon pyrrole, (4) the oxidation of alkyl pyrroles with fused potassium hydroxide (oxidation with potassium permanganate causes disruption of the molecule). The α-acids are further obtainable from the pyrryl magnesium halides (see p. 481), and also from the α-methyl-pyrroles by treatment with sulphuryl chloride, and hydrolysis of the intermediate trichloro compound:[1]

Decarboxylation of the carboxylic acid gives the pyrrole with a hydrogen atom in the α position and the reaction thus provides a method for the elimination of an α-methyl group.

Like the pyrrole ketones, the pyrrole carboxylic acids, and particularly their esters, are relatively stable. The α-carboxylic acids readily lose their carboxyl group on heating (frequently on boiling with water), the β- are more stable. The esters of the α-carboxylic acids are also much more readily hydrolysed by alkali than the β-, but the reverse is the case when hydrolysis is carried out by means of concentrated sulphuric acid at 40–60°.

Pyrrole α-carboxylic acids when heated with acetic anhydride give dimolecular anhydrides, 'Pyrokolle' (I), while certain β-carboxylic acids under the same circumstances give coloured substances (II) analogous to anthraquinone:

The pyrrole β-carboxylic acids are considerably weaker than the α-carboxylic acids.

Alkylated pyrroles may be prepared in variety by the various modifications of Knorr's synthesis, the nuclear carbethoxy groups being subsequently removed by hydrolysis and decarboxylation. They may also be prepared from the pyrrole aldehydes and ketones by reduction with hydrazine and sodium ethoxide (Wolff-Kishner method, see p. 394).

[1] H. Fischer, E. Sturm, and H. Friedrich, *Annalen*, 1928, **461**, 270.

Alkyl groups may be introduced into the pyrrole nucleus (1) by heating potassium pyrrole with alkyl iodides, when the intermediate N-alkyl-pyrrole is converted into the alkylated (usually α-) pyrrole; (2) by heating already alkylated pyrroles with a sodium alkoxide at 210–220°:

(3) by the action of alkyl or aryl halides on pyrryl magnesium halides; (4) by passing the vapour of pyrrole itself and an alcohol over heated zinc dust.

One of the more interesting facts about the alkyl pyrroles is that certain of them are the main reduction products obtained by the action of hydriodic acid or phosphonium iodide and hydriodic acid on the colouring matters of blood, such as haemin, and of plants, such as chlorophyll, and also of the bile, such as bilirubin. The four principal compounds so formed are shown below, together with their common names. The structures of all of them have been established by synthesis.

3-Methyl-4-ethyl-pyrrole
Haemopyrrole

2,3-Dimethyl-4-ethyl-pyrrole
Isohaemopyrrole

2,4-Dimethyl-3-ethyl-pyrrole
Kryptopyrrole

2,3,5-Trimethyl-4-ethyl-pyrrole
Phyllopyrrole

The homologues of pyrrole show the typical properties of pyrrole itself, but are, in general, less reactive and more stable. Those pyrroles which contain a free α-position produce an intense red colour in the cold with Ehrlich's reagent, which is a solution of p-dimethylamino-benzaldehyde in dilute hydrochloric acid. The aldehyde condenses with the pyrrole in the α-position to give a pyrrolenine compound (III); the red colour is due to the salt of this product. Its kation is like that of a triphenylmethane

dye, in that two structures can be written, in one of which the pyrrole ring is quinonoid and in the other the benzene ring is quinonoid. There is no difference between the structures except in the distribution of the electrons, and we find the same intense absorption owing to the resonance between the two structures, which has been discussed earlier (see p. 93).

$$\text{[pyrrole]} + OCH \cdot C_6H_4 \cdot NMe_2 \longrightarrow \text{[structure]} =CH-\text{[ring]}-NMe_2 \quad (III)$$

$$\text{[structure]} =CH-\text{[ring]}-NMe_2 \quad \text{and} \quad \text{[structure]}-CH=\text{[ring]}=\overset{+}{N}Me_2$$

Pyrroles with only a β-position free and tetra-substituted pyrroles scarcely give the reaction even on heating, unless an easily eliminated group such as carbethoxyl or carboxyl is present in the α-position.

Fission of the pyrrole nucleus is more difficult than fission of the furane nucleus which may be opened by methyl alcoholic hydrogen chloride to give the acetal of succindialdehyde.

$$\begin{array}{c} CH\text{---}CH \\ \| \quad\quad \| \\ CH \quad\quad CH \\ \diagdown O \diagup \end{array} \longrightarrow \begin{array}{c} CH_2\text{------}CH_2 \\ | \quad\quad\quad | \\ CH(OMe)_2 \, CH(OMe)_2 \end{array}$$

Direct hydrolysis of pyrrole should give succindialdehyde and ammonia, but an equilibrium seems to be set up between the pyrrole and the hydrolysis products in which the former predominates.

$$\text{[pyrrole]} + 2H_2O \rightleftharpoons \begin{array}{c} CH_2\text{---}CH_2 \\ | \quad\quad | \\ CHO \quad CHO \end{array} + NH_3$$

In the presence of hydroxylamine, however, which combines with the dialdehyde, alkaline hydrolysis proceeds smoothly.[1] Thus 2,5-dimethyl-pyrrole gives the dioxime of acetonylacetone, and 2,4-dimethylpyrrole gives the dioxime of methyl-laevulinic aldehyde.

$$CH_3\text{[ring]}CH_3 \longrightarrow CH_3-\underset{\underset{NOH}{\|}}{C}\begin{array}{c}CH_2\text{---}CH_2\\ \end{array}\underset{\underset{NOH}{\|}}{C}-CH_3$$

$$CH_3\text{[ring]}CH_3 \longrightarrow \begin{array}{c}CH_3-CH\text{---}CH_2\\ | \quad\quad | \\ \underset{NOH}{CH} \quad \underset{NOH}{C}-CH_3\end{array}$$

Hydrolysis and identification of the dicarbonyl compound gives an obvious method for the orientation of the alkyl groups in the original pyrrole.

[1] G. Ciamician, *Ber.* 1904, **37**, 4200.

Oxidation of pyrroles also provides an important method for the orientation of alkyl groups in the nucleus, and has been used in the degradation of both the cleavage products of the porphyrins, and the porphyrins themselves. The oxidation is carried out with chromic-sulphuric acid mixture. Pyrrole itself gives maleic imide, β-substituted pyrroles give substituted maleic imides, whilst an α-substituent is oxidized to carboxyl and eliminated.

Many of these maleic imides are important reference substances in porphyrin chemistry, e.g. methylethylmaleic imide and haematinic acid (methylmaleic imide-β-propionic acid).

Pyrrole undergoes an interesting reaction when its potassium derivative is heated with chloroform in presence of sodium ethoxide; it is converted into β-chloropyridine.

Other halogen derivatives act in the same way, the new carbon atom becoming the β-carbon atom of the pyridine nucleus. Thus bromoform gives β-bromopyridine, benzalchloride gives β-phenylpyridine, methylene iodide gives pyridine itself. The reaction takes place with many homologues of pyrrole and with indoles.

The conversion of a pyrrole into a pyridine can also take place in another way. If an N-alkyl or an α-alkyl-pyrrole is passed through a heated tube, the group enters the nucleus. Thus N-benzylpyrrole gives β-phenylpyridine:

and α-methylpyrrole gives pyridine.

As has been mentioned already, the action of acids on pyrrole brings about polymerization. The formula for pyrrole, as usually written, contains the conjugated system —C=C—C=C—, but there is no addition of maleic anhydride to the 1,4-positions of the system, as in a normal Diels-Alder reaction which does occur with the oxygen analogue furan. In the case of α-methylpyrrole addition takes place with the formation of 2-methylpyrrole-5-succinic acid (I), which readily loses carbon dioxide to form 2-methylpyrrole-5-propionic acid. In the case of pyrrole itself the reaction is more complicated and gives the di-succinic acid corresponding to (I) along with decarboxylation and hydrolysis products.[1]

---

[1] *Ann. Reports C. S.* 1933, **226** et seq.

$$\text{Me}\!-\!\underset{\text{NH}}{\boxed{}} + \underset{\text{CH--CO}}{\overset{\text{CH--CO}}{\Big\rangle}}\!\!O \longrightarrow \text{Me}\!-\!\underset{\text{NH}}{\boxed{}}\!\!\underset{\overset{|}{\text{CH}_2\!-\!\text{CO}_2\text{H}}}{\text{CH--CO}_2\text{H}} \qquad \text{I.}$$

In acid solution, however, the aromatic properties of pyrrole are destroyed to a large extent, a point which is discussed in greater detail below, and the compound shows the same tendency to polymerize which is found in many unsaturated hydrocarbons of similar structure, such as cyclopentadiene.

$$\begin{array}{ccc} \text{CH} & \!\!-\!\! & \text{CH} \\ \| & & \| \\ \text{CH} & & \text{CH} \\ & \diagdown\!\!\diagup & \\ & \text{CH}_2 & \end{array}$$

A large variety of polymers of increasing complexity can be obtained, some amorphous and some crystalline, but the majority cannot be purified and are mixtures and not single substances. The best-known definite compound is tripyrrole, which is obtained as its hydrochloride,

$$(C_4H_5N)_3,HCl,$$

by treating an ethereal solution of pyrrole with hydrogen chloride, or as colourless crystals of the free base by neutralizing a solution of pyrrole in dilute hydrochloric acid with ammonia. When heated, it decomposes at 300° into ammonia, pyrrole, and indole. Various structures have been proposed for it, such as the following:

Neither of these is satisfactory, because they fail to explain its decomposition to indole. The polymerization of cyclopentadiene has been studied in detail by K. Alder and G. Stein,[1] who have shown that it involves addition of the double bond of one molecule to the 1,4-positions of the conjugated system of another, and have demonstrated that the di- and tri-polymers are formed in the following way:

[1] *Annalen*, 1931, **485**, 223; 1932, **496**, 204.

In view of these facts it seems certain that the polymerization of pyrrole takes a similar course and that the tripolymer contains two bridged rings. As is shown below, such a structure will account satisfactorily for the decomposition products formed on heating.[1]

In the case of 2,3-dialkyl-, 2,3,4-trialkyl-, and the tetra-alkylpyrroles, dimolecular polymers can be isolated. They resemble the dipolymer of cyclopentadiene in that they depolymerize on heating; their structures are almost certainly of the following type:

The Structure of Pyrrole. It will have become evident from the preceding section that pyrrole is a typical aromatic compound, and that its most outstanding peculiarity is its failure to exhibit normal basic properties. This absence of normal basic properties has been attributed by W. Marckwald[2] to the fact that the NH group is attached to two —C=C— groups, in support of which may be cited the weakly basic character of the NH groups in, for example, diphenylamine and carbazole, both of which readily give potassium derivatives.

Such an explanation, however, can only indicate why pyrrole should be a weak base, and whilst it may thus offer a partial explanation of the peculiar behaviour of pyrroles towards acids, it cannot account for the fact that when pyrrole does combine with an acid the whole character and reactivity of the substance is changed. Thus pyrrole itself is precipitated as a polymer on the addition of alkali to its solution in cold dilute acid, and, in general, strong acids rapidly cause resinification. It therefore seems

[1] This suggestion was made by R. Robinson at a meeting of the Chemical Society in Oxford, Oct. 1935.   [2] *Annalen,* 1894, **279**, 8; *Ber.* 1895, **28**, 114, 1501.

that in the form of its salts pyrrole reacts as a highly unsaturated, olefinic compound, which rapidly undergoes self-condensation.

Bamberger in 1891 suggested that a centric formula for pyrrole could be written if the nitrogen atom were supposed to contribute two valencies (I), and that this might account for the absence of basicity, since the nitrogen would have no valencies left for salt formation.

Put into electronic terms this simply means that if six electrons are required in some manner to make up aromatic character and stability, then such a structure can exist in pyrrole only if the lone pair of electrons of the nitrogen atom are part of this structure (II), and they are, therefore, not available to accept a proton in the process of salt formation, unless the aromatic character of the substance is destroyed. It may be noted that in the case of pyridine which is basic (III) six electrons are available without calling upon the lone pair on the nitrogen atom.

Such a view does not, however, prove satisfactory when extended to other cyclic systems. A striking example of this is to be found in indole and iso-indole; the former shows the characteristic stability of an aromatic compound, while attempts to prepare the latter have failed, although both compounds have the same atoms in a ring of the same size, and their formulae could be written with the requisite six electrons for an aromatic system.

Indole   Iso-indole

With benzene a more acceptable view is that the aromatic character does not arise from some special configuration of six 'free' electrons, but from the presence of a closed conjugated system of three double bonds. Benzene is essentially a resonance-hybrid of the various states of the molecule which arise from the possible distributions of these double bonds. If this view is adopted, it is natural to assume a somewhat similar state of affairs in pyrrole, and the assumption leads to a structure which is in good agreement with the properties of the compound. The formula of pyrrole can be written in five different ways which differ from one another only in the distribution of the electrons; they are shown in the following formulae, in which the dots represent unshared electrons.

Of these the first is Baeyer's formula and the remainder represent zwitterions, in which the nitrogen atom is positively charged and one carbon atom is negatively charged.[1] There is the possibility of resonance between all these forms, just as there is between the two Kekulé formulae for benzene, and pyrrole is best regarded as the resonance-hybrid of these forms. Such a view not only accounts for the aromatic nature of pyrrole, but also for the fact that it shows no true basic properties; it is almost legitimate to describe the nitrogen atom as partly positively charged in the free compound, so that its tendency to unite with a proton must clearly be reduced. Further, if pyrrole is forced to form a salt, the unshared electrons become shared, and the resonating states are no longer possible. As we have already seen, under these conditions the aromatic properties disappear and pyrrole behaves as a highly unsaturated substance.

It should be noted that those pyrroles which are capable of salt formation without polymerization are always those which contain 'negative' substituents, such as phenyl, acyl, or ester groups, which themselves possess unshared electrons, and are presumably capable of acting as electron donors. The constitution of the characteristic, stable pyrrole picrates is unknown, but it is very probable that they are not true salts of the NH group, but possess the picric acid combined with some other part of the molecule, since aromatic hydrocarbons form similar complexes with picric acid and other polynitrophenols.

Another peculiarity in the chemistry of pyrroles is the fact that they will undergo both α- and β-substitution with almost equal ease. The electronic formulae may provide a partial explanation of this, but the explanation may also lie in the fact that pyrrole can exist, or at least react, in the so-called pyrrolenine (pseudo-pyrrole) forms:

as is evidenced by the formation of iso-nitroso and iso-nitro derivatives, alkyl derivatives containing two alkyl groups united to one carbon atom, ketonic forms of hydroxy-pyrroles, &c. This pseudo-pyrrole structure also occurs in the pyrrylmethenes (p. 482) and in the porphyrins.

Reduction Products of Pyrrole

Pyrrole can take up two or four atoms of hydrogen, giving pyrroline and pyrrolidine respectively; the former can exist theoretically in three different modifications, the latter only in one.

Δ^1-Pyrroline Δ^2-Pyrroline Δ^3-Pyrroline   Pyrrolidine

[1] They have been discussed by C. K. Ingold, *J.C.S.* 1933, 1120.

Reduction of pyrrole with zinc dust and acetic or hydrochloric acid gives Δ^3-pyrroline, whose structure is proved by ozonolysis of its hydrochloride in dilute aqueous solution, followed by treatment with hydrogen peroxide, when iminodiacetic acid is obtained.[1]

$$
\begin{array}{c}
\text{H}\overline{\quad\quad}\text{H} \\
\text{H}_2\boxed{\quad\quad}\text{H}_2 \\
\text{NH}
\end{array}
\xrightarrow{\text{O}_3}
\begin{array}{c}
\text{HO}_2\text{C}\quad\text{CO}_2\text{H} \\
| \qquad | \\
\text{CH}_2\quad\text{CH}_2 \\
\diagdown\diagup \\
\text{NH}
\end{array}
$$

It is probable that all pyrrolines produced by reduction of pyrroles are of the Δ^3-type. They are stable compounds, exhibiting strong basic properties, and showing no tendency to polymerize. Their further reduction to pyrrolidines is somewhat difficult, but may be effected by means of hydriodic acid and phosphorus, hydrogen in presence of nickel at 190°, or hydrogen in presence of a platinum catalyst in acetic acid solution.

Δ^1-Pyrrolines are unknown as individuals; they are possibly tautomeric with the Δ^2-pyrrolines which are available by a number of synthetical reactions, such as the action of ammonia on γ-bromoketones:

$$
\begin{array}{c}
\text{CH}_2\text{—CH}_2 \\
| \qquad | \\
\text{BrCH}_2\quad\text{CO—CH}_3
\end{array}
+ \text{NH}_3 \longrightarrow
\begin{array}{c}
\text{H}_2\overline{\quad\quad}\text{H} \\
\text{H}_2\boxed{\quad\quad}\text{CH}_3 \\
\text{NH}
\end{array}
$$

and they may also be prepared by the action of a Grignard reagent on α-pyrrolidones.

$$
\begin{array}{c}
\text{H}_2\overline{\quad\quad}\text{H}_2 \\
\text{H}_2\boxed{\quad\quad}\text{CO} \\
\text{NH}
\end{array}
+ \text{RMgX} \longrightarrow
\begin{array}{c}
\text{H}_2\overline{\quad\quad}\text{H} \\
\text{H}_2\boxed{\quad\quad}\text{R} \\
\text{NH}
\end{array}
$$

The Δ^2-pyrrolines are less stable than the Δ^3-pyrrolines. They resinify easily on exposure to the air, and are readily reduced to pyrrolidines by treatment with tin and hydrochloric acid.

Pyrrolidine may be prepared by the reduction of the pyrrolines as already mentioned, or more conveniently by the reduction of pyrrole itself. Reduction may be effected in various ways; with hydriodic acid and phosphonium iodide at 240–250°; with hydrogen in presence of nickel at 200°;[2] or in presence of platinum in acetic acid solution.[3] Pyrrolidines may also be prepared by electrolytic reduction of succinimide or its alkyl substitution products.

$$
\begin{array}{c}
\text{CH}_2\text{—CO} \\
| \qquad\qquad \diagdown \\
\text{CH}_2\text{—CO} \diagup
\end{array}\!\!\text{NH}
\quad\longrightarrow\quad
\begin{array}{c}
\text{CH}_2\text{—CH}_2 \\
| \qquad\qquad \diagdown \\
\text{CH}_2\text{—CH}_2 \diagup
\end{array}\!\!\text{NH}
$$

Pyrrolidine can be synthesized from open-chain compounds in various ways: (i) from 1,4-dibromobutane by the action of p-toluenesulphon-

[1] A. Treibs and D. Dinelli, *Annalen*, 1935, **517**, 170.

[2] M. Padoa, *Atti R.* 1906, **15**, 219; N. J. Putochin, *Ber.* 1922, **55**, 2742.

[3] R. Willstätter and D. Hatt, ibid. 1912, **45**, 1477; K. Hess, ibid. 1913, **46**, 3120.

amide, and hydrolysis of the resulting N-p-toluenesulphonyl derivative, (ii) from δ-chlorobutylamine by the elimination of hydrogen chloride under the influence of alkali,[1] (iii) in small quantity by the reduction of ethylene dicyanide, accompanied by tetramethylene diamine, (iv) by distillation of the dihydrochloride of tetramethylene diamine (see p. 468).

$$
\begin{array}{ll}
\text{i.} & \begin{array}{l}CH_2 \cdot CH_2 \cdot Br \\ | \\ CH_2 \cdot CH_2 \cdot Br\end{array} \searrow \\[2em]
\text{ii.} & \begin{array}{l}CH_2 \cdot CH_2 \cdot Cl \\ | \\ CH_2 \cdot CH_2 \cdot NH_2\end{array} \longrightarrow \quad \begin{array}{l}CH_2{-}CH_2 \\ | \qquad\quad \rangle NH \\ CH_2{-}CH_2\end{array} \\[2em]
\text{iv.} & \begin{array}{l}CH_2 \cdot CH_2 \cdot NH_3Cl \\ | \\ CH_2 \cdot CH_2 \cdot NH_3Cl\end{array} \nearrow
\end{array}
$$

An interesting production of an α-methylpyrrolidine derivative from piperidine is described by G. Merling.[2] Piperidine combines with methyl iodide to give dimethylpiperidinium iodide, which reacts with moist silver oxide to give the corresponding hydroxide (I). On distillation this loses water and forms the open-chain, unsaturated tertiary base (II). Addition of hydrogen chloride to (II) produces (III), which readily passes into the methochloride of 1,2-dimethylpyrrolidine (IV), in its turn decomposed on heating into 1,2-dimethylpyrrolidine (V).

$$
\begin{array}{l}CH_2{-}CH_2{-}N(CH_3)_2[OH] \\ | \qquad\qquad\quad | \\ CH_2{-}CH_2{-}CH_2\end{array} \longrightarrow \begin{array}{l}CH_2{-}CH_2{-}N(CH_3)_2 \\ | \\ CH_2{-}CH{=}CH_2\end{array}
$$
$$
\text{I.} \qquad\qquad\qquad\qquad\qquad \text{II.}
$$

$$
\longrightarrow \begin{array}{l}CH_2{-}CH_2{-}N(CH_3)_2 \\ | \\ CH_2{-}CHCl{-}CH_3\end{array}
$$
$$
\text{III.}
$$

$$
\begin{array}{l}CH_2{-}CH_2 \\ | \qquad\quad \rangle NCH_3 \\ CH_2{-}CH\langle \\ \qquad\qquad CH_3\end{array} \longleftarrow \begin{array}{l}CH_2{-}CH_2 \\ | \qquad\quad \rangle N(CH_3)_2[Cl] \\ CH_2{-}CH\langle \\ \qquad\qquad CH_3\end{array}
$$
$$
\text{V.} \qquad\qquad\qquad\qquad\qquad \text{IV.}
$$

Pyrrolidine is a strong secondary base, possessing a pungent ammoniacal odour. It absorbs carbon dioxide from the air and is miscible with water. It exhibits all the properties of an aliphatic secondary base and shows no tendency to polymerize in presence of acids.

The pyrrolidine ring may be opened in various ways. The 'exhaustive methylation' process of Hofmann, which ultimately converts the carbon

[1] Putochin, loc. cit. p. 2747.
[2] *Annalen,* 1891, **264,** 310; 1894, **278,** 1.

chain of pyrrolidine into butadiene, is illustrated by the following reactions.

$$\begin{array}{c}CH_2\!-\!CH_2 \\ | \qquad\qquad \\ CH_2\!-\!CH_2\end{array}\!\!\!\!\diagdown\!\!NH \quad \xrightarrow[-HI]{2CH_3I} \quad \begin{array}{c}CH_2\!-\!CH_2 \\ | \qquad\qquad \\ CH_2\!-\!CH_2\end{array}\!\!\!\!\diagdown\!\!N(CH_3)_2[I]$$

$$\xrightarrow[H_2O]{Ag_2O} \quad \begin{array}{c}CH_2\!-\!CH_2 \\ | \qquad\qquad \\ CH_2\!-\!CH_2\end{array}\!\!\!\!\diagdown\!\!N(CH_3)_2[OH] \quad \xrightarrow[-H_2O]{distil} \quad \begin{array}{c}CH_2\!-\!CH_2\!-\!N(CH_3)_2 \\ | \qquad\qquad\qquad\quad \\ CH\!=\!CH_2\end{array}$$

$$\xrightarrow[Ag_2O]{CH_3I} \quad \begin{array}{c}CH_2\!-\!CH_2\!-\!N(CH_3)_3[OH] \\ | \qquad\qquad\qquad\quad \\ CH\!=\!CH_2\end{array} \quad \xrightarrow{distil} \quad \begin{array}{c}CH\!=\!CH_2 \\ | \qquad\qquad \\ CH\!=\!CH_2\end{array} + (CH_3)_3N + H_2O$$

In a similar way β-methylpyrrolidine gives isoprene,

$$CH_2\!:\!C(CH_3)\!\cdot\!CH\!:\!CH_2$$

and it was by this method that isoprene was first synthesized.[1] The method is generally applicable to cyclic nitrogen-containing ring systems, where the nitrogen is not doubly bound as in pyridine or quinoline; e.g. piperidine yields α-methylbutadiene, the double bonds in the hydrocarbon becoming conjugated during the final stage of the process. It has been very frequently used in determining the constitution of the natural alkaloids.

The pyrrolidine ring may also be opened by the action of a phosphorus pentachloride or bromide, on N-benzoyl-pyrrolidine, which yields 1,4-dichloro- or dibromobutane and benzonitrile.[2]

$$\begin{array}{c}CH_2\!-\!CH_2 \\ | \qquad\qquad \\ CH_2\!-\!CH_2\end{array}\!\!\!\!\diagdown\!\!N\!\cdot\!CO\!\cdot\!\phi \longrightarrow \begin{array}{c}CH_2\!-\!CH_2 \\ | \qquad\qquad \\ CH_2\!-\!CH_2\end{array}\!\!\!\!\diagdown\!\!N\!\cdot\!CCl_2\phi \longrightarrow \begin{array}{c}CH_2\!-\!CH_2Cl \\ | \qquad\qquad\quad \\ CH_2\!-\!CH_2Cl\end{array} + NC\!\cdot\!\phi$$

Piperidine similarly yields the pentamethylene dihalides, and the method is chiefly valuable as a means of preparing such polymethylene halides, which are valuable synthetical agents.

A further method of opening the pyrrolidine ring is by the action of cyanogen bromide on an N-alkylpyrrolidine; this gives at once an unstable addition product which spontaneously undergoes rearrangement to give an open-chain compound.[3]

$$\begin{array}{c}CH_2\!-\!CH_2 \\ | \qquad\qquad \\ CH_2\!-\!CH_2\end{array}\!\!\!\!\diagdown\!\!NR + CN\!\cdot\!Br \longrightarrow \begin{array}{c}CH_2\!-\!CH_2 \\ | \qquad\qquad \\ CH_2\!-\!CH_2\end{array}\!\!\!\!\diagup\!\!\diagdown\!\!\!\!\begin{array}{c}R \\ N \\ CN\end{array}[Br]$$

$$\longrightarrow \begin{array}{c}CH_2\!-\!CH_2Br \\ | \qquad\qquad\quad \\ CH_2\!-\!CH_2\!\cdot\!NR\!\cdot\!CN\end{array}$$

The method may also be used in the case of piperidine, but the reaction does not proceed as easily as in the case of pyrrolidine.

Derivatives of Pyrrolidine. A few only of the more important of these substances will be mentioned.

[1] W. Euler, *Ber.* 1897, **30**, 1989.

[2] J. v. Braun and E. Beschke, ibid. 1906, **39**, 4119.

[3] J. v. Braun, ibid. 1909, **42**, 2219; 1911, **44**, 1252.

Pyrrolidine α-carboxylic acid (proline) occurs in its laevorotatory modification as a product of hydrolysis of many proteins, and was first isolated by E. Fischer from the hydrolysis products of casein. The inactive acid has been synthesized in a number of ways, for example by condensing trimethylene dibromide with sodiomalonic ester to give δ-bromo-propyl-malonic ester, brominating this in the α-position, and treating with ammonia, when the diamide of pyrrolidine-dicarboxylic acid is formed; the latter when heated with hydrochloric acid gives proline.[1]

$$CH_2Br \cdot CH_2 \cdot CH_2Br + NaCH(CO_2Et)_2 \longrightarrow CH_2Br \cdot CH_2 \cdot CH_2 \cdot CH(CO_2Et)_2$$

$$\longrightarrow CH_2Br \cdot CH_2 \cdot CH_2 \cdot CBr(CO_2Et)_2$$

$$\longrightarrow \begin{array}{c} CH_2—CH_2 \\ | \quad\quad | \\ CH_2 \quad C(CO_2NH_2)_2 \\ \diagdown \diagup \\ NH \end{array} \longrightarrow \begin{array}{c} CH_2—CH_2 \\ | \quad\quad | \\ CH_2 \quad CH \cdot CO_2H \\ \diagdown \diagup \\ NH \end{array}$$

The racemic acid was resolved in the form of its N-*m*-nitrobenzoyl derivative by recrystallization of the cinchonine salt.[2]

4-Hydroxy-pyrrolidine-2-carboxylic acid (hydroxy-proline) (VI) is also a hydrolysis product of many proteins; it contains two non-identical asymmetrical carbon atoms and can therefore exist in two different racemic forms. All the four optically active forms have been obtained by synthesis.[3]

$$\begin{array}{c} HO \cdot CH—CH \\ | \quad\quad | \\ CH_2 \quad CH \cdot CO_2H \\ \diagdown \diagup \\ NH \\ \text{VI.} \end{array} \quad\quad \begin{array}{c} CH_2—CH_2 \\ | \quad\quad | \\ CH_2 \quad CH \cdot CH_2 \cdot CO \cdot CH_3 \\ \diagdown \diagup \\ NCH_3 \\ \text{VII.} \end{array} \quad\quad \begin{array}{c} CH_2—CH_2 \\ | \quad\quad | \\ CH_2 \quad CH \cdot CO_2H \\ \diagdown \diagup \\ NCH_3 \\ \text{VIII.} \end{array}$$

$$\begin{array}{c} CH_2—CH_2 \\ | \quad\quad | \\ CH_2 \quad CH—CO_2^- \\ \diagdown \diagup \\ \overset{+}{N}(CH_3)_2 \\ \text{IX.} \end{array}$$

Pyrrolidine derivatives are sometimes obtained by the degradation of certain alkaloids. Thus, oxidation of hygrine, itself N-methyl-2-acetonyl-pyrrolidine (VII), yields N-methylpyrrolidine-2-carboxylic acid (VIII), the methyl betaine of which is the naturally occurring alkaloid stachydrine (IX). Oxidation of tropine and ecgonine with chromic acid gives two tropinic acids (X), which differ only in the fact that the former is optically inactive and the latter dextrorotatory; on oxidation they both yield N-methylsuccinimide, and by exhaustive methylation followed by reduction they yield *n*-pimelic acid.

Examples of the ketopyrrolidines or pyrrolidones are the lactams or

[1] R. Willstätter, *Ber.* 1900, **33**, 1160: *Annalen*, 1903, **326**, 91.
[2] E. Fischer and G. Zemplén, *Ber.* 1909, **42**, 2992.
[3] H. Leuchs and K. Bormann, ibid. 1919, **52**, 2086.

internal amides of the γ-amino-acids, such as butyrolactam (α-pyrrolidone) (XI).

$$CH_2\text{—}CH_2$$
$$HO_2C\cdot CH \quad CH\cdot CH_2\cdot CO_2H$$
$$NCH_3$$

X.

$$CH_2\text{—}CH_2$$
$$CH_2 \quad CO$$
$$NH$$

XI.

$$CH_2\text{—}CH_2$$
$$HO_2C\cdot CH \quad CO$$
$$NH$$

XII.

$$CH_2\text{—}CH_2$$
$$CO \quad CH\cdot CH_2\cdot CO_2H$$
$$NCH_3$$

XIII.

Such compounds behave like acid amides, and may be conveniently prepared by electrolytic reduction of succinimides (themselves 2,5-diketo-pyrrolidines). 2-Ketopyrrolidine-5-carboxylic acid (XII) is obtained by the cyclization of glutamic acid, and has been isolated from the products of hydrolysis of horn; it is probably formed in this case also from glutamic acid. 1-Methyl-2-ketopyrrolidine-5-acetic acid (ecgoninic acid) (XIII) is produced by oxidation of tropine, ecgonine, or tropinic acid.

INDOLE AND ITS SIMPLER DERIVATIVES

If a pyrrole ring and a benzene ring are united to give a condensed system, two isomeric benzopyrroles might be expected, since the rings could be fused together in the 2,3-positions of the pyrrole nucleus, as in (I), or in the 3,4-positions, as in (II). The former compound (I) is indole, by far the more important of the two isomers; the formula shows how the positions of substituents in indole derivatives are indicated, either by numbers or, when in the heterocyclic ring, by the prefixes N-, α-, and β-.

The second compound (II) is called iso-indole and can be dismissed briefly. Neither the compound itself nor any of its simple derivatives (except dihydro derivatives) are known.

I.

II.   →   III.

Indeed, the ortho-quinonoid structure (II) could hardly be expected to exist, because by a simple migration of a hydrogen atom it could pass over into the pseudo-iso-indole structure (III), in which there is a true aromatic benzene nucleus. Even the pseudo-iso-indole system is very difficult to prepare; the only simple example of such a structure appears to be the methyl derivative (IV), which has been described by S. Gabriel and A. Neumann[1] as an oil, characterized by a number of derivatives, but unstable in the free state or in presence of acids. It was prepared by the

[1] Jbid. 1893, 26, 521, 705.

reduction by means of zinc and hydrochloric acid, of chloromethylphthal-azine (V), which is obtained from methylphthalazone by the action of phosphorus oxychloride.[1] The instability of the iso-indole structure, as compared with that of indole, seems to arise from the fact that with this arrangement of the atoms there is no possibility of resonance between a number of different states, so that a true aromatic system cannot be formed.[2] Methyl-pseudo-iso-indole is nothing but the internal Schiff's base of o-aldehydo-methylbenzylamine (VI), and, as such, is unstable in the presence of acids. An interesting compound in which both the true iso-indole structure and the pseudo-iso-indole structure can be said to occur is phthalocyanine. This contains four iso-indole units united by nitrogen atoms into a ring, and forms intensely coloured, stable and insoluble derivatives with many metals.[3] Dihydro-iso-indoles are relatively easy to prepare; one method is by the action of ammonia or primary amines on o-xylylene dibromide.[4]

IV.   V.   VI.

Indole is the parent substance of a large number of important com-pounds which occur in nature. Examples are indigo and hetero-auxin, which are discussed below, and the amino-acid tryptophane (see p. 125). Indole itself occurs in jasmine and orange-flower oils and is found together with some homologues in the fraction of coal-tar which boils between 240° and 260°. It can be isolated from this fraction as its solid sodium or potassium derivative, just as pyrrole can be isolated from a lower-boiling fraction. β-Methylindole (skatole) is produced during the pancreatic diges-tion or putrefactive decomposition of albuminous substances, and is there-fore found in the intestines and faeces; it also occurs in civet, and in certain plants.

Indole is a crystalline solid, melting at 52° and boiling at 245° with decomposition. It is obtained from its oxygen-containing derivatives such as indigo or indoxyl by distillation with zinc dust (A. von Baeyer, 1866–8), or treatment with sodium amalgam. It has been synthesized in a number of ways, of which the following are the more important.

(1) Treatment of o-amino-ω-chlorostyrene with sodium ethylate.

[1] For other attempts to obtain pseudo-iso-indoles see G. W. Fenton and C. K. Ingold, *J.C.S.* 1928, 3295; J. Malan and R. Robinson, ibid. 1927, 2653.

[2] C. K. Ingold, ibid. 1933, 1127.

[3] R. P. Linstead and collaborators, ibid. 1934, 1016 et seq.

[4] M. Scholtz, *Ber.* 1898, **31**, 1707.

(2) The action of alcoholic potash on the dibromide of N-acetyl o-amino-styrene:[1]

$$\text{[structure: benzene ring with } CHBr\cdot CH_2Br \text{ and } NH\cdot COMe] \longrightarrow \text{[indole, NH]} + 2HBr + Me\cdot CO_2H.$$

(3) Reduction of o-nitrocinnamic acid or of o-nitrophenylacetaldehyde.

$$\text{[ring with } CH:CH\cdot CO_2H \text{ and } NO_2] \longrightarrow \text{[ring with } CH:CH\cdot CO_2H \text{ and } NHOH]$$

$$\longrightarrow \text{[ring with } CH, \; C\cdot CO_2H, \; NH] \longrightarrow \text{[indole, NH]} + CO_2$$

$$\text{[ring with } CH_2CHO \text{ and } NO_2] \longrightarrow \left[\text{ring with } CH:CHOH \text{ and } NH_2\right] \longrightarrow \text{[indole, NH]} + H_2O$$

(4) Reduction of o-nitrophenylacetonitrile with stannous chloride and hydrogen chloride in dry ether, followed by hydrolysis with water;[2] this probably takes place by ring closure of the amino-aldehyde.

$$\text{[ring with } CH_2\cdot CN \text{ and } NO_2] \longrightarrow \text{[ring with } CH_2\cdot CH:NH \text{ and } NH_2]$$

$$\longrightarrow \text{[ring with } CH_2\cdot CHO \text{ and } NH_2] \longrightarrow \text{[ring with } CH, CH, NH]$$

(5) Indole is also formed to a small extent by passing the vapour of N-methyl-o-toluidine together with hydrogen over finely divided nickel at 300°. This reaction is reversible, and indole may, in the same way, be partially reduced to N-methyl-o-toluidine.

Derivatives of indole may be prepared by several general reactions. In one of these aniline is allowed to react with an α-halogenated ketone; the reaction probably involves the following stages:[3]

$$2\phi\cdot NH_2 + \begin{array}{l}CH_2Cl \\ | \\ CO\cdot CH_3\end{array} \longrightarrow \text{[ring—N=C(CH}_3)\text{—CH}_2\cdot NH\phi]$$

$$\longrightarrow \text{[ring with } CH, \; C\cdot CH_3, \; NH] + \phi\cdot NH_2.$$

This method is of wide application, since different substituted arylamines and alkylanilines can be employed.

[1] T. W. J. Taylor and P. M. Hobson, *J.C.S.* 1936, 181.

[2] H. Stephen, ibid. 1925, **127**, 1874.   [3] A. Bischler, *Ber.* 1892, **25**, 2860.

✗ The most important general method was discovered by Emil Fischer and involves the elimination of ammonia from the phenylhydrazones, or substituted phenylhydrazones, of a great variety of aldehydes, ketones or ketonic acids. Thus the phenylhydrazone of acetone yields α-methyl-indole:

$$+ NH_3.$$

The usual condensing agents for this reaction are zinc chloride, alcoholic hydrochloric acid, dilute sulphuric acid, and glacial acetic acid. With some phenylhydrazones the reaction takes place with the greatest ease; cyclohexanone phenylhydrazone can be converted into tetrahydrocarbazole in excellent yield by merely warming with aqueous hydrochloric acid. At first sight the reaction appears to involve the elimination of ammonia from the middle of a chain, but it undoubtedly involves a number of intermediate steps. Various suggestions have been made as to the mechanism of the reaction, but most of them can be shown to be erroneous. Thus the view that the first stage is an ortho-semidine transformation, which is followed by ring closure with loss of ammonia is clearly untenable, because, as is shown in the equation below, it would mean that a substituent in position 4 of the benzene ring would become a substituent in position 6 of the indole, and it is known that this does not happen.

The most satisfactory proposal is that of R. Robinson and G. M. Robinson.[1] This provides an adequate explanation of the facts, and each stage postulated is similar to a reaction which is known to take place in other cases. The series of reactions they suggest is that in the first stage the hydrazone rearranges to an o-amino-phenylethylene-amine probably through the intermediate hydrazine which is obviously a tautomer of the hydrazone. This stage is analogous to the ortho-benzidine rearrangement, which is known to occur in some cases (see p. 386). The final stage is that the diamine undergoes ring closure with elimination of ammonia (as ammonium salt), and this is parallel to the formation of cyclic imines from the dihydrochlorides of 1,4- and 1,5-diamines (see p. 468).

[1] J.C.S. 1918, **113**, 639; 1924, **125**, 827.

It was on the basis of this scheme that the remarkable synthesis of tetra-phenylpyrrole described on p. 477 was predicted. One case where the Fischer indole reaction fails is for the preparation of indole itself. According to the general scheme of the reaction it should be formed from the phenylhydrazone of acetaldehyde, but none is obtained.

The synthesis proceeds even more readily when secondary hydrazines, such as *asymm*-methylphenylhydrazine, are employed, the products being N-alkylindoles:

The reaction may also be applied to the production of indole carboxylic acids, e.g. an *asymm*-alkylphenylhydrazone of pyruvic acid is readily converted into the N-alkylindole-α-carboxylic acid even by dilute hydro-chloric acid:

It should be noted that derivatives of β-keto-acids, such as acetoacetic ester, generally react with phenylhydrazine to give pyrazolones, and only occasionally indoles.

$$\phi \cdot NH—N:C(CH_3) \cdot CH_2 \cdot CO_2Et \longrightarrow$$

If the reaction is extended to aldehydes and ketones containing a tertiary carbon atom adjacent to the CO group, the product is a derivative of the tautomeric indolenine form of indole:

whilst with the same ketonic component, an *asymm*-alkylphenylhydrazine gives a derivative of dihydro-indole.

Indoles may also be prepared by the action of sodamide on the N-acyl derivatives of *o*-toluidine:

Indole resembles pyrrole in many respects. It is only very feebly basic, and polymerizes in the presence of acids; prolonged action of acids converts it into a resin. These facts seem to indicate that the constitution of the pyrrole nucleus in indole is similar to that of pyrrole itself, and involves resonance between a number of states of which some are zwitterions. Solutions of indole produce a bright cherry-red colour on a pine shaving which has been moistened with alcohol and hydrochloric acid.

The homologues of indole are similar to indole, but are more stable towards acids. Many of them, and especially skatole (β-methyl indole), possess objectionable odours. The α-alkyl indoles give the pine shaving reaction easily, but with the β-alkyl compounds it is not so readily obtained; a red colour which changes to violet is formed if the usual procedure is reversed, and the pine shaving is moistened with an alcoholic solution of the β-alkyl indole and then dipped in strong hydrochloric acid. The $\alpha\beta$-dialkyl indoles give no pine shaving reaction whatever. When alkyl indoles are fused with potash, they are oxidized to indole carboxylic acids. Most indoles give crystalline picrates.

With acid anhydrides, aromatic diazo compounds, and esters of nitrous acid, the indoles react like the pyrroles, but the substituent nearly always enters the β-position, and only seldom the α-position, so that the normal product is the β-acyl, -benzeneazo, or -nitroso derivative, respectively. With chloroform and sodium ethoxide indole gives a mixture of the β-aldehyde and β-chloroquinoline, a reaction similar to that of pyrrole.

Grignard reagents are decomposed by indoles and an indolyl magnesium halide is formed. The constitution of these compounds is almost certainly similar to that of the corresponding pyrryl compounds, with the magnesium atom attached to nitrogen. The indolyl magnesium halides are useful synthetical reagents; they give an aldehyde when treated with formic ester and ketones with acid chlorides, but again the substituent enters the β-position, and not the α-position as is the case in many reactions of pyrryl derivatives. Certain indole aldehydes and ketones can be obtained by the Gattermann and Hoesch reactions, that is, by the action of hydrogen cyanide or of a nitrile on the indole in ethereal solution in presence of hydrogen chloride.

Dihydro-indole, or indoline, can be made by reducing N-methyl indole with zinc and hydrochloric acid to N-methyl indoline, and heating this with hydriodic acid and phosphorus, whereby the methyl group is eliminated. It can also be prepared directly from indole by electrolytic reduction or by catalytic hydrogenation; the latter reduction may proceed as far as octahydro-indole. Indoline is a colourless liquid which shows none of the typical behaviour of an indole. It is a base, and its reactions are those of a secondary aromatic-aliphatic amine.

Of the carboxylic acids which contain the indole nucleus, indole-β-acetic acid (I) is of special interest, because of the part it can play in the physiology of plants. The process of growth in the growing tip of a plant is regulated by the presence of certain compounds, the growth hormones. It

C·CH$_2$·CO$_2$H

CH

NH

I.

CH

N CH $+$ Cl·CH$_2$·CN $\longrightarrow$

MgI

II.

C·CH$_2$·CN

CH

NH

is also these substances which determine the well-known behaviour of a plant in growing towards the light and away from the ground: differences of concentration of the compounds in the different parts of the shoot make the parts grow at different rates, and hence determine the direction of growth.[1] Substances which have these properties are called auxins, and so far three have been obtained from natural sources. Auxin a has been isolated from maize seedlings and also from urine, while auxin b, which has the same activity, occurs in plants but has not been found in urine;[2] these two compounds contain no nitrogen and are, respectively, a trihydroxy-acid and a hydroxy-ketonic acid. The third substance, called hetero-auxin, which has about half the activity of the other two, has been isolated from urine and has been shown by the brilliant work of Kögl and his collaborators in Utrecht to be indole-β-acetic acid.[3] It does not seem to occur in the higher plants, but can be detected in yeast and certain moulds, although, strangely enough, it does not behave as a growth factor to the moulds. Indole-β-acetic acid has been synthesized by the action of indolyl magnesium iodide on chloroacetonitrile in ether followed by hydrolysis with potash (II).[4] If heated above its melting-point (165°), it loses carbon dioxide readily and gives β-methyl indole (skatole). The occurrence of the compound in urine is not surprising, since it has been known for some time that it is formed by bacterial action on tryptophane, a constituent of protein (p. 125).[5] The growth-hormone property of heteroauxin does not seem to depend on the fact that it is an acid, since skatole (β-methyl indole) also promotes the growth of an oat seedling.[6]

[1] An interesting account by F. A. F. C. Went can be found in *Naturwiss.* 1933, **21,** 1.

[2] General account by F. Kögl, ibid. 1933, **21,** 17; K. V. Thimann, *Ann. Rev. Biochem.* 1935, **4,** 545.

[3] *Z. physiol. Chem.* 1934, **228,** 90, 104, 113.

[4] R. Majima and T. Hoshino, *Ber.* 1925, **58,** 2042.

[5] C. A. Herter, *J. biol. Chem.* 1908, **4,** 253.

[6] J. Glover, *Nature,* 1936, **137,** 320.

The Hydroxy-indoles

The story of these compounds is so closely connected with the discovery of the structure of indigo that it will be convenient to approach them from that point of view. Indigo is probably the oldest known dye-stuff and naturally attracted the attention of chemists at an early date. Its volatility and bronzy lustre are very striking, and at one time the latter was thought to indicate something of a metallic nature. In a more scientific age the desire to elucidate its structure was stimulated by the hope of discovering a method for the artificial preparation of this valuable dye. The ultimate solution of the problem was mainly due to the genius of Adolf von Baeyer, and it forms one of the most interesting chapters in the history of organic chemistry.[1] Baeyer had been fascinated by indigo as a child and spent most of the money given him on his thirteenth birthday in buying a lump of the dye-stuff.

The first observation of importance was the discovery by O. L. Erdmann and A. Laurent in 1841 that indigo is oxidized by chromic acid or nitric acid to a compound $C_8H_5NO_2$ which was named isatin, after one of the plants from which indigo can be obtained (see below). This was clearly a benzene derivative, since further oxidation with strong nitric acid gave picric acid, but nothing further was known at that time about the compound. In 1868 Baeyer published a description of the products he obtained by the reduction of isatin in a paper which is the first in the first volume of the *Berichte der deutschen chemischen Gesellschaft*. These products were dioxindole and its reduction product oxindole; this last was further reduced to an oxygen-free compound, indole, by passing its vapour over hot zinc dust, a method introduced here for the first time and adopted immediately afterwards by C. Graebe and C. Liebermann for the conversion of alizarin into anthracene, which led to the synthesis of alizarin. Baeyer suspected that indole was related to pyrrole and proceeded to establish the constitution of both substances. It was known that isatin would dissolve in alkali to give a salt of an acid, isatinic acid, formed by addition of a molecule of water to one of isatin. In 1869 A. Kekulé suggested that isatinic acid was amino-benzoyl formic acid (III) and isatin its internal amide or lactam (IV), and that it might be synthesized from o-amino-phenylacetic acid (VII). He was, however, unable to prepare that acid. Baeyer realized later that if Kekulé was right, the reduction products of isatin might be similarly related to other simple amino-acids, (V) and (VII). He eventually proved the truth of these views, firstly by showing that acetyl-isatinic acid, in which the closure of the pyrrole ring is inhibited by the acetyl group, can be reduced to o-acetylamino-mandelic acid (N-acetyl derivative of (V)), and secondly by synthesizing o-nitrophenylacetic acid and showing that on reduction it gives oxindole via the unstable o-amino-

o-Amino-benzoyl
formic acid

III.

Isatin

IV.

ψ-Isatin

IX

o-Amino-mandelic acid

V.

Dioxindole

VI.

X.

o-Amino-phenylacetic
acid

VII.

Oxindole

VIII.

XI.

acid (VII). Since he found he could oxidize oxindole to isatin and had already prepared indigo from isatin, this was the first synthesis of indigo (6 June 1878).

Oxindole and dioxindole need little discussion; they are clearly 2-hydroxy-indole (XI) and 2,3-dihydroxy-indole (X), respectively, but these are simply enolic forms of the ketonic structures (VIII) and (VI) which Baeyer allotted to them and which agree with the majority of their reactions. There is also the possibility of another tautomerism in these compounds between the lactam and lactim structures,

$$\text{—NH—CO—} \rightleftharpoons \text{—N=C(OH)—},$$

and this is mentioned later in the case of isatin.

Another hydroxy-indole, the 3-derivative, clearly should exist. This is called indoxyl and its ketonic and enolic formulae are shown in (XII) and (XIII). The compound was not isolated in a pure state until 1902,[1]

Indoxyl

XII.

XIII.

XIV.

because it shows the remarkable property of being oxidized to indigo by the air, especially in the presence of alkali. Nearly all the syntheses of indigo that are known are really syntheses of indoxyl or indoxyl carboxylic acid. The method of preparation is to heat an aqueous solution of indoxyl carboxylic acid (see p. 509) in the complete absence of oxygen: carbon

[1] D. Vorländer and B. Drescher, *Ber.* 1902, **35**, 1701.

dioxide is lost and indoxyl crystallizes out on cooling. The acid sulphate derived from the enolic form (XIV) occurs under certain conditions as its alkali salts in the urine of mammals and, on standing, is converted into indigo.

Isatin[1] (IV and IX), a bright orange-red solid, is a derivative of 2,3-dihydro-indole. The most direct evidence of its constitution is its synthesis by L. Claisen and J. Shadwell[2] who succeeded in carrying out Kekulé's suggestion. They obtained o-nitrobenzoyl chloride and converted it successively into the cyanide and the sodium salt of o-nitrophenylglyoxylic acid: this was reduced to the amino-acid, which when set free passed rapidly into isatin.

$O_2N \cdot C_6H_4 \cdot COCl$

$$\longrightarrow \quad O_2N \cdot C_6H_4 \cdot CO \cdot CN \quad \longrightarrow \quad \text{[structure]} \overset{-CO \cdot CO_2H}{\underset{-NH_2}{}} \quad \longrightarrow \quad \text{isatin.}$$

Apart from its connexion with indigo, it is of industrial importance as an intermediate in the manufacture of a large number of vat dye-stuffs.[3] The two most important commercial processes for its synthesis are extremely ingenious and are due to T. Sandmeyer. In each the various stages give practically quantitative yields, and only cheap and readily accessible materials are used. They can both be used for the preparation of isatins with substituents in the benzene ring, some of which are valuable intermediates.

The first method consists of four stages. The first is the formation of diphenyl-thiourea (p. 292) from aniline and carbon disulphide: in the second stage the thio-urea is treated with lead carbonate and hydrogen cyanide, which gives N,N'-diphenylcyano-formamidine: in the next stage this is converted with yellow ammonium sulphide into a thio-amide. The latter is finally treated with 96 per cent. sulphuric acid at 105°, when it undergoes a remarkable reaction; sulphur, sulphur dioxide, and ammonium sulphate are formed together with a quantitative yield of isatin-α-anilide. This compound can be hydrolysed to isatin and aniline or, as mentioned later, converted into indigo.

$$\underset{\phi NH}{\overset{\phi NH}{}} \!\!\!\! {>}CS \longrightarrow \underset{\phi NH}{\overset{\phi N}{}} \!\!\!\! {>}C \cdot CN$$

$$\longrightarrow \underset{\phi NH}{\overset{\phi N}{}} \!\!\!\! {>}C \cdot CS \cdot NH_2 \longrightarrow \text{[structure]} \overset{-CO}{\underset{NH}{\overset{|}{C}=N \cdot \phi}}$$

The second process can be applied to any aniline, but not to naphthyl-amines. The amine is treated in the presence of water with chloral and hydroxylamine sulphate[4] when oximino-acetanilide is formed: this is

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[1] A useful monograph is 'Über Isatin, etc.' by G. Heller, *Ahrens' Sammlung*, vol. **5**, (Neue Folge), 1931.   [2] *Ber.* 1879, **12**, 350.

[3] See H. E. Fierz-David, *Künstliche Organische Farbstoffe*, Berlin, 1926, p. 458 et seq.   [4] T. Sandmeyer, *Helv. Chim. Acta*, 1919, **2**, 234.

converted by solution in strong sulphuric acid into isatin-β-imide, which is hydrolysed to isatin and ammonia by diluting with water.

$\phi NH_2 + Cl_3C \cdot CHO + NH_2OH$

$\longrightarrow$ [benzene ring]—NH·CO·CH:NOH $\longrightarrow$ [benzene ring with fused ring: NH, CO, C=NH]

Towards most reagents isatin behaves as the lactam (IV), though, on alkylation with silver oxide and an alkyl iodide, O-alkyl ethers derived from the lactim form (IX) can be obtained. It is claimed as the first recognized case of a tautomeric substance, and to account for its behaviour Baeyer in 1882 suggested that both lactam and lactim forms were always present. It was at one time thought that in solution the compound was almost entirely in the lactam form, because its absorption spectrum was held to resemble that of its N-methyl ether and to differ from that of the O-methyl ether. More accurate work, however, has shown that all three compounds have very similar absorption spectra,[1] and consequently the point remains in doubt. The reactivity of the two :CO groups is very different. The one next to the nitrogen atom behaves like the :CO group of an amide and is much less reactive than the other. The β-carbonyl group is truly ketonic and condenses readily with compounds containing a reactive methylene group: thus with acetone the compound

[benzene ring with fused ring]—C:CH·CO·CH₃ / CO / NH

can be obtained. With isatin-α-anilide, however, the position is reversed and condensation takes place preferentially on the α-carbon atom with elimination of aniline. It is for this reason that the anilide is so valuable as a dye-stuff intermediate.

Indigo

The structure of indigo (perhaps more correctly described as indigotin) follows very easily when that of isatin is known. The vapour density shows the molecular formula to be $C_{16}H_{10}O_2N_2$, and, since oxidation gives nothing but isatin, it is clearly composed of two units, each of which oxidizes to isatin. The only question remaining is how the two units are attached. There are three possibilities:

[structure: two benzene rings with CO, NH, C=C groups]

Indigo

[structure: Iso-indigo]

Iso-indigo

[1] R. G. Ault, E. L. Hirst, and R. A. Morton, *J.C.S.* 1935, 1653.

Indirubin

Baeyer showed that in indigo the two units are united by an $\alpha\alpha'$-link, by synthesizing indigo from a compound which contains the carbon skeleton, $\phi \cdot C \cdot C \cdot C \cdot C \cdot \phi$. This was di-o-nitrophenyl-diacetylene, which with strong sulphuric acid undergoes rearrangement to di-isatogen, and this is reduced by ammonium sulphide to indigo.

The same point is also clearly shown by the nature of break-down products from indigo obtained by the action of strong alkali.[1] They are anthranilic acid and indoxyl-α-aldehyde.

Finally Baeyer showed that there were two imino groups present by synthesizing the N-diethyl compound and showing that its properties resemble those of indigo. Hence indigo must be allotted the formula shown above.

The two isomers of indigo are known; the $\beta\beta'$-compound, iso-indigo, is formed by condensing isatin with oxindole and is not a dye-stuff. The $\alpha\beta'$-compound, indirubin, can similarly be obtained from isatin and indoxyl; it occurs in natural indigo in small amount and is a red compound.

Indigo is a dark-blue substance which takes on a coppery lustre when rubbed. It is insoluble in water, acids, alkalis and alcohol, is somewhat soluble in chloroform and acetic acid, and more soluble in pyridine, molten phenol, and hot aniline, from which it can be recrystallized. It can be sublimed without decomposition under reduced pressure and gives a purple vapour. The solution in aniline is red and its molecular weight in this

[1] P. Friedländer and E. Schwenk, *Ber.* 1910, **43**, 1971.

solvent is normal. The p-toluidine solutions are blue and show twice the expected molecular weight at the freezing-point of p-toluidine (45°), but the normal value at the boiling-point (198°). The crystals of p-toluidine that separate on freezing are colourless, so that there is no question of the results being vitiated by the formation of a solid solution.

Indigo has been used as a dye-stuff since the earliest times, and until the beginning of this century the sources from which it was obtained were certain plants, the more important of which were *Indigofera tinctoria* and *Polygonum tinctorium*, which were cultivated in India and Java. The actual compound which occurs in these plants is the glucoside indican, a compound of glucose and indoxyl, which can be isolated from the leaves of the plants. It has been prepared synthetically by condensing the sodium derivative of the enolic form of the methyl ester of indoxyl carboxylic acid with tetra-acetyl α-glucosidyl bromide and removing the acetyl and carboxyl groups.[1]

When the plant is broken up and treated with water, the glucoside is hydrolysed to indoxyl, probably with the aid of an enzyme, indimulsin, which can be extracted from the leaves. The indoxyl is oxidized by the air mainly to indigo, although some isatin is also formed which condenses with the indoxyl to indirubin. The presence of this latter was.for some time believed to make natural indigo superior to the synthetic product, but it is now known that indirubin is unstable to alkalis and is destroyed during the dyeing operations. The production of natural indigo was reduced to very small proportions when the synthetic product became available, except for a temporary revival during the earlier stages of the Great War when synthetic indigo, at that time only manufactured in Germany, was not available outside that country. Indigo can also be obtained from woad (*Isatis tinctoria*), a European plant which does not contain indican but another glucoside, isatan, the constitution of which has not yet been elucidated.

Indigo is the best known example of a vat-dye, that is to say, a substance which itself is incapable of combining with textile fibres, but which can be reduced to a compound which has that property and, after combination with the fibre, can be oxidized back to the colouring matter. How knowledge of this operation was first obtained is unknown. The ancient method was the so-called fermentation vat, in which vegetable matter was allowed to stand with water and produce compounds of reducing properties such as the monosaccharoses. Possibly bacterial action was also involved in the reduction. Later, lime and zinc dust were used, or lime and ferrous sulphate, but the reducing agent which is almost universally used nowadays is an

[1] A. Robertson, *J.C.S.* 1927, 1937.

alkaline solution of sodium hydrosulphite ($Na_2S_2O_4$) or its compound with formaldehyde, sodium formaldehyde-sulphoxylate, which is technically known as rongalite. The reduction product, indigo white, is a colourless compound which is soluble in alkali and will combine with fibres of all kinds.

Indigo white

The material to be dyed absorbs this leuco-compound, and is then rinsed with water and exposed to the air, when indigo is formed.

As a dye-stuff indigo has many merits and some demerits. It is much faster to light and washing than many substances that have been used as dyes, but it does not combine completely with either vegetable or animal fibres, e.g. cotton or wool. Part of the dye seems to be merely precipitated in the fibre so that the colour is not fast to continual rubbing: the looseness of the combination is shown by the fact that indigo can be quantitatively extracted from a textile with pyridine or glacial acetic acid. It has been for long the most important dye-stuff, the amount used annually in the world is about 10 million kilograms, but its importance seems to be on the wane. It has serious competitors in other dye-stuffs of more recent introduction, such as those of the indanthrene group, which are superior to it in several ways.

An interesting derivative of indigo arose from the desire to produce the dye-stuff in such a form that reduction to the vat in the dye-works was unnecessary. Various preparations of indigo white, stabilized with compounds such as glucose, have been used, but the most valuable is obtained by the action of the pyridine salt of chlorosulphonic acid on indigo white. The pyridine salt of the half ester of sulphuric acid results, from which the sodium salt can be obtained. This is called indigosol: it is soluble in water and combines with cotton fibre, but is quite stable to atmospheric oxygen: it is oxidized to indigo by mild oxidizing agents, such as a dilute solution of nitrous acid.

Indigosol

It can also be prepared directly from indigo by the action of copper in the presence of sulphur trioxide and pyridine. The advantage of a compound

with these properties is that by its use indigo can be easily printed on to a fabric.

The development of the commercial manufacture of indigo is one of the classics of industrial organic chemistry. Baeyer himself discovered many ways by which the compound could be synthesized, but by none of them could it be produced at a sufficiently low price to compete with the natural product. This was chiefly because in his processes the indole structure was completed by closing the ring between positions 1 and 2, and thus necessitated ortho-nitro compounds which clearly were expensive, because their

formation was accompanied by that of the para compound. The successful methods of commercial synthesis close the ring between the carbon atom in position 3 and the benzene ring. That such a synthesis is possible was first indicated by the observation of W. Flimm,[1] that by the action of alkali on ω-bromacetanilide oxindole can be obtained.

Very soon after this K. Heumann[2] showed that phenylglycine and phenylglycine-o-carboxylic acid give, when fused with alkali, indoxyl and indoxyl carboxylic acid, respectively; these are oxidized by the air to indigo, the latter with the loss of carbon dioxide.

The yields from the o-carboxylic acid were better than those from the unsubstituted compound, so the Badische Anilin und Soda Fabrik developed the latter method. The starting-point was naphthalene, a cheap substance because its uses are few, which was oxidized to phthalic anhydride with strong sulphuric acid: the accidental breaking of a thermometer during this operation showed that mercuric sulphate was a valuable catalyst. The sulphur dioxide formed in the oxidation can be reconverted into sulphuric acid by the contact process.

The action of gaseous ammonia on the molten anhydride gives phthalimide which is converted into anthranilic acid by sodium hypochlorite

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[1] *Ber.* 1890, **23**, 57.   [2] Ibid. 3048, 3431.

(a Hofmann reaction). Condensation with chloracetic acid, the production of which involved the first commercial use of liquid chlorine, gives phenylglycine-*o*-carboxylic acid, which is converted into indigo as shown above.

By this process, which was widely used at one time, indigo was first produced on the commercial scale. Various improvements have been made. The oxidation to phthalic anhydride can be carried out by air with vanadium pentoxide as catalyst at 440–480°. The stage anthranilic acid → phenylglycine carboxylic acid can be carried out by using formaldehyde and hydrogen cyanide (a Strecker reaction, p. 117), and hydrolysing the nitrile so formed.

$$C_6H_4{<}^{NH_2}_{CO_2H} + CH_2O + HCN \longrightarrow C_6H_4{<}^{NH \cdot CH_2 \cdot CN}_{CO_2H}$$

The great advance in the process came, however, from a study of the last stage, the alkali-fusion. A German firm which manufactured cyanides from sodamide, seeking fresh outlets for sodamide, found that if that compound were substituted for caustic soda or potash, the ring closure took place at 200° instead of 300°, and the yields of indigo were much improved. Further, it was found that if all water is carefully excluded, the yield was almost quantitative, not only with the *o*-carboxylic acid, but also with phenylglycine itself. The discovery of these two facts led to the process which is most widely used to-day. The starting-point is aniline, which is converted into phenylglycine with chloroacetic acid. The carefully dried sodium salt of the latter, $\phi \cdot NH \cdot CH_2 \cdot CO_2Na$, is fused with a mixture of sodamide and sodium oxide, obtained by heating caustic soda *in situ* with ammonia at 300°, together with more than sufficient metallic sodium to combine with the water formed in the ring closure. Alternatively, phenylglycine can be made via its nitrile from aniline, formaldehyde, and hydrogen cyanide by a method similar to that mentioned for phenylglycine-*o*-carboxylic acid. This is obviously a useful variant in countries where hydrogen cyanide is produced on a large scale for the destruction of insect pests. Another variation of the synthesis is to condense aniline with ethylene chlorhydrin, which can be obtained from ethylene and bleaching-powder. The resulting β-phenylamino-ethyl alcohol is an oil, and it is pumped into a fused mixture of sodium and potassium hydroxides, which must be as free as possible from water and carbonates. The heating is carried out in an atmosphere of hydrogen. Dihydro-indole is formed by ring closure and is oxidized to

the sodium salt of indoxyl; gaseous hydrogen is evolved during this stage and is pumped off and used in subsequent preparations.

$$\phi \cdot NH_2 + Cl \cdot CH_2 \cdot CH_2OH \longrightarrow \phi NH \cdot CH_2 \cdot CH_2 \cdot OH$$

The only other technically possible process for the synthesis of indigo is that of Sandmeyer which has been described above for the preparation of isatin-α-anilide. This compound can be easily converted into indigo in good yield and without separating the free compound. Its solution in concentrated sulphuric acid is allowed to flow into water together with a solution of sodium hydrogen sulphide. α-Thio-isatin is precipitated and, when treated with an alkali, gives a mixture of indigo and sulphur. Though Sandmeyer's process has been used for isatin, it has never been applied on any scale to the production of indigo.

An enormous number of substitution products and other derivatives of indigo have been prepared, and many of them are useful dye-stuffs. The only one which will be mentioned here is 6,6'-dibromo-indigo, which is the compound called Tyrian purple, or the purple of the ancients. Certain shell-fish (notably *Murex brandaris* and *M. trunculus*) in the Mediterranean Sea secrete a colourless liquid, and this on exposure to light and air gives the purple dye which was so prized in classical times. P. Friedländer[1] showed that in composition and behaviour it corresponded to a dibromo-indigo, and when he synthesized the 6,6'-compound it proved identical with the natural product. On the fabric it gives a somewhat dull reddish violet colour. The occurrence of an indigo in shell-fish is not surprising, but that of a dibromo-substituted compound is very striking. Friedländer's preparation of the compound was as follows:

The characteristic properties of indigo, and in particular its stability

[1] *Ber.* 1909, **42**, 765.

and colour, do not at first sight seem to be adequately explained by the formula which Baeyer established for it. Consequently many attempts to emend the formula have been made, but few of them have any real significance. Since the formula contains a true ethylenic double bond, indigo might exist in two geometrically isomeric forms.

trans   *cis*

Only one form is known and since in a structure of this kind the *trans* form would be expected to be more stable than the *cis*, the *trans* form has been generally accepted for indigo. This view is fully confirmed by the investigation of the structure of crystalline indigo with X-rays.[1] The results show that the molecule of indigo must possess a centre of symmetry, and this is only possible if the configuration is *trans*. The same point is illustrated by the fact that indigo condenses with phenylacetic ester to give a dye-stuff of the following formula:[2]

Ring closure of this kind would be difficult with the *cis* indigo. Since in the *trans* structure carbonyl and imino groups are comparatively near to one another, the suggestion has often been made that the interaction of these groups may be concerned with the peculiar properties of indigo. Some of these suggestions seem to overlook two important facts; the first is that N,N'-dimethylindigo, which can be prepared from N-methylphenylglycine carboxylic acid, is a green dye closely resembling indigo in its properties; the second is that the —NH— groups of indigo can be replaced by sulphur atoms (—S—) to give thio-indigo, which also resembles indigo very closely in its behaviour. These facts show that the presence of a hydrogen atom attached to nitrogen is in no way necessary for the development of indigoid properties.

The essential truth of Baeyer's structure of indigo is perhaps best shown by the properties of certain other compounds which contain the same elements in their structure, i.e. carbonyl groups connected through double bonds to imino groups which are members of a ring. A good example is indanthrene blue R which R. Bohn discovered in 1901. He was trying to prepare dye-stuffs of a mixed anthraquinone-indigo type by ring closure from β-anthraquinonylglycine.

[1] A. Reis and W. Schneider, *Z. Krist.* 1928, **68**, 543.

[2] T. Posner and W. Kemper, *Ber.* 1924, **57**, 1311.

A blue dye was obtained but it soon was found that the same substance was formed in better yield from β-amino-anthraquinone and that its structure is:

Indanthrene blue resembles indigo in being a very stable, intensely coloured vat-dye. Further, the introduction of substituents in either molecule produces alterations in colour of the same kind, and there seems no doubt that the origin of the dye-properties is the same in the two compounds. This may be taken as support for Baeyer's structure. At the same time, however, the problem of the relation between structure and properties in this group is by no means settled. A. D. Ainley and R. Robinson[1] have pointed out that another group of compounds should exist which are closely related to indigo and contain the same elements of structure. The mother substance, epindolidione, might, in fact, be formed in many of the known indigo syntheses. Thus in Baeyer's synthesis from di-*o*-nitrophenyldiacetylene there are two possibilities of ring closure, one giving indigo and the other epindolidione. Similarly in the ingenious synthesis of indigo from dianilino-fumaric acid,[2] ring closure might take place in two ways:

Indigo

Epindolidione

One epindolidione has been synthesized, the 4,10-dimethyl derivative. It

[1] *J.C.S.* 1934, 1508.   [2] A. Salmony and H. Simonis, *Ber.* 1905, **38**, 2580.

is a yellow infusible substance, only soluble in hot pyridine and quinoline, and shows no vat dye-stuff properties at all, in spite of the close structural relationship to indigo.

There is a further possible modification of Baeyer's formula which has been suggested by R. Kuhn.[1] He considers that the insolubility of indigo and its association in certain solvents may indicate that the molecule is an internal salt:

He further suggests that such a structure is taken up because the positive and negative charges will lie close together in space, their position corresponding to that of two adjacent members of a five-membered ring. With this formula the molecule does not contain any aromatic nuclei; both the benzene rings have become ortho-quinonoid. In this respect an attractive modification of his view presents itself. There are many examples of dye-stuffs in which the origin of the colour seems to be resonance between structures, in some of which a benzene ring is truly aromatic, and in others it is quinonoid; examples discussed in this book are the triphenylmethane dyes and the cyanine dyes (pp. 93 and 561). Hence indigo might be a resonance-hybrid of the Baeyer structure and Kuhn's quadripole, and the view could be extended to thio-indigo, since the sulphur could become positively charged as in the sulphonium salts. The evidence is insufficient to determine whether this is involved in the true solution to the problem. It suffers from the defect that it offers no obvious explanation for the fact that indigo is red in solvents such as aniline and decalin, in which it is monomolecular, and is blue when the molecules are associated. Finally Kuhn's suggestion that the close proximity of the charges in the internal salt structure may be connected with the characteristic properties of indigo does not seem to be borne out by the behaviour of compounds such as (XV), which has been prepared by P. Friedländer and F. Risse.[2] This compound and the related thio compound are both vat-dyes, which differ from indigo and thio-indigo only in their fastness and not in their colour. The fine structure of indigo is a problem which still awaits solution.

CARBAZOLE

Carbazole, is dibenzo-pyrrole, and occurs in the crude

anthracene from coal-tar. It can be extracted from this source by

[1] *Naturwiss.* 1932, **20**, 618. [2] *Ber.* 1914, **47**, 1919.

fusion with potash, which converts the carbazole into its N-potassium derivative.

It can also be obtained by passing the vapour of diphenylamine through a hot tube:

and by the elimination of ammonia, under the influence of acids, from *o,o'*-diamino-diphenyl:

A valuable synthetical method, applicable to the preparation of a number of carbazole derivatives, is to act upon *o*-amino-diphenylamine with nitrous acid, and to heat the N-phenylbenzotriazole so formed; nitrogen is evolved and carbazole remains:

Carbazole melts at 238°, and, like pyrrole, exhibits no pronounced basic properties. It is a very stable compound and is not attacked by strong sulphuric acid below 300°. It behaves like a secondary amine in forming an N-nitroso derivative when its solution in glacial acetic acid is treated with sodium nitrite.

SIX-MEMBERED RINGS

ONLY the rings containing one nitrogen atom will be considered here. The saturated ring consisting of five methylene ($>CH_2$) groups and an imino group ($>NH$) is piperidine, while pyridine is the aromatic compound related to piperidine just as benzene is related to cyclohexane. The pyridine ring is found condensed with a benzene ring, just as two benzene rings are condensed in naphthalene, but there are two possibilities because of the position of the nitrogen atom, and these are quinoline and isoquinoline. These compounds will be discussed in some detail. The compounds with a pyridine ring condensed with more than one benzene ring (acridine, phenanthridine) are dealt with briefly.

PYRIDINE

(A useful reference book is by H. Maier-Bode and J. Altpeter, *Das Pyridin und seine Derivate in Wissenschaft und Technik*, 1934.)

The aromatic pyridine nucleus is not often found in nature, but it forms part of the alkaloid nicotine which is *l*-1-methyl-2-β-pyridylpyrrolidine (I). The fully reduced compound piperidine is, however, of fairly frequent

$$CH_2—CH_2$$

$$\text{—CH} \quad CH_2$$

$$N \qquad NMe$$

I.

occurrence in natural products. Pyridine was discovered by T. Anderson, who, during the years 1845–51, isolated it from bone oil, together with picoline (methylpyridine) and lutidine (dimethylpyridine). Bone oil is produced by the dry distillation of bones, which still contain their natural fat. The formation of these bases from animal matter requires the presence of unsaponified fats, since if the fats are removed, pyrroles are formed, but no pyridines; while if free fatty acids are present they are converted into the corresponding nitriles. It would seem, therefore, that the production of pyridine derivatives only occurs in the presence of glycerol. This is converted at a high temperature into acrolein, which combines with the ammonia formed from the nitrogenous matter (gelatine, &c.) to give pyridine bases. Pyridine bases have since been found amongst the products of distillation of many kinds of nitrogenous organic matter, and the source from which they are now usually isolated is coal-tar.

It was early realized that the chemical behaviour of pyridine, in particular its great stability and general similarity to benzene, could only

be explained by a ring formula, and the following structure was advanced by W. Körner in 1869 and by J. Dewar in 1871:

$$
\begin{array}{c}
\text{CH} \\
\text{CH} \quad \text{CH} \\
\text{CH} \quad \text{CH} \\
\text{N}
\end{array}
$$

This formula is supported by numerous syntheses of pyridine and its derivatives. It gives no representation of the true nature of the aromatic nucleus, a problem which presents itself here just as acutely as with benzene. The formula must not be interpreted as suggesting one particular arrangement of the double bonds; in no case are the two isomeric α-mono-substituted pyridines known which such a view would imply. This fact is parallel with the non-existence of the two isomeric ortho-disubstitution products of benzene. The latter is probably best regarded as a resonance-hybrid of the two possible Kekulé forms,

and the identity of all the links in the ring is shown by the complete symmetry of the benzene ring in compounds such as durene.[1] A similar state of affairs almost certainly obtains in pyridine, and the Körner-Dewar formula must be interpreted in that light.

The positions of substituents in the nucleus of pyridine are indicated either by the prefixes N, α, β, and γ (II), or by numbers (III), and the formula of pyridine is frequently written as a simple hexagon with a nitrogen atom at one of the angles (IV).

II.   III.   IV.

A mono-substituted pyridine can exist in three isomeric forms, a di-substituted pyridine in six forms if both substituents are identical, but in twelve if the substituents are not identical.

Syntheses of Pyridine and Derivatives

No attempt is made here to give an exhaustive account of the very numerous pyridine syntheses. A brief description only will be given of those reactions which are of importance either because of their synthetical value, or from theoretical interest.[2]

[1] J. M. Robertson, *Proc. Roy. Soc.* 1933, **142**, A, 659.

[2] A valuable summary of the synthetical methods up to 1924 will be found in *The Synthesis of Nitrogen Ring Compounds*, by C. Hollins, E. Benn, Ltd., 1924.

(i) A simple synthesis of pyridine consists in the oxidation of piperidine, itself prepared by heating the hydrochloride of pentamethylene diamine.

$$NH_2 \cdot (CH_2)_5 \cdot NH_2 \longrightarrow$$

The oxidation is carried out by heating either with concentrated sulphuric acid at 300°, or with nitrobenzene at 260°, or with silver acetate in acetic acid; the production of pyridine in this way affords a clear proof of its fundamental structure.

(ii) Alkylated pyridines are produced by heating aldehyde-ammonias either alone or with aldehydes or ketones. Thus acetaldehyde-ammonia and acetaldehyde yield 2-methyl-5-ethylpyridine (aldehyde collidine):

$$\longrightarrow \quad + 4H_2O.$$

A similar reaction is the formation of β-picoline by heating glycerol with phosphorus pentoxide and a derivative of ammonia such as acetamide or ammonium phosphate. The reaction probably involves the intermediate formation of acrolein:

$$\longrightarrow \quad + 2H_2O.$$

The β-picoline produced by the dry distillation of animal substances is doubtless formed in this way. These methods of preparing pyridines are of little synthetical value, chiefly owing to the fact that a mixture of pyridine bases is generally obtained.

(iii) A reaction of wide application is A. Hantzsch's pyridine synthesis, in which two molecules of a β-diketone or a β-ketonic ester are combined with one molecule of an aldehyde and one molecule of ammonia, or one molecule of an aldehyde-ammonia: thus with an ester of acetoacetic acid and aldehyde-ammonia the reaction may be represented as follows:

V.   VI.

Collidine

The intermediate products in this reaction are undoubtedly an alkylidene-β-ketonic ester (V) (the ammonia acting as the condensing agent between the aldehyde and the β-ketonic ester) and a β-amino-crotonic ester (VI), since both these substances can be, and frequently are, directly employed in the synthesis. It will be noted that the initial product of the reaction is a dihydropyridine derivative (in this case dihydrocollidine dicarboxylic ester), which must then be oxidized with a suitable oxidizing agent (e.g. nitrous fumes) to give the true pyridine derivative, from which any carboxyl groups may be eliminated by heating with lime.

The Hantzsch synthesis of pyridines gives excellent yields and is capable of great variation since a variety of β-keto-esters and aldehydes may be employed. Further, it can be modified by replacing part of the acetoacetic ester by an aldehyde, when a mono-carboxylic ester is formed. In this case the dihydro compound first formed is oxidized during the course of the reaction, and the actual product which is obtained in 25–30 per cent. yield is the true pyridine. Thus acetoacetic ester reacts with two molecules of acetaldehyde and one of ammonia to give 2,4-dimethylpyridine-3-carboxylic ester.

Other similar condensations also yield true pyridine derivatives; examples are the interaction of an amino-crotonic ester with an ethoxymethylene-acetoacetic ester or an ethoxymethylene-ketone,[1]

[1] L. Claisen, *Ber.* 1893, **26**, 2729.

and the condensation of an acylpyruvic ester with an amino-crotonic ester.[1]

$$\underset{\underset{\underset{NH_2}{|}}{\underset{MeC}{\|}}}{EtO_2C \cdot CH} \qquad \underset{\underset{CO \cdot R}{|}}{\underset{CH_2}{\overset{CO \cdot CO_2Et}{|}}} \longrightarrow$$

Another reaction very similar to that of Hantzsch is due to E. von Meyer. A so-called 'dinitrile', really an unsaturated amino-nitrile formed by condensing, for example, benzonitrile with acetonitrile in presence of sodium (see p. 315), is condensed with, say, acetoacetic ester in presence of hydrogen chloride, the product being a derivative of γ-hydroxy-pyridine:

(iv) A reaction recalling the preparation of pyrroles from ammonia and 1,4-diketones is the formation of pyridine by the action of ammonia on certain unsaturated 1,5-diketones prepared, for example, by the condensation of an ethoxy-methylene-acetoacetic ester with a β-ketonic ester. The reactions are represented by the following scheme:

Very similar is the conversion of saturated 1,5-diketones, particularly those containing ·CO·φ groups, into pyridines by the action of hydroxylamine:

[1] O. Mumm and H. Hüncke, *Ber.* 1917, **50**, 1573; Θ. Mumm and O. Böhme, ibid. 1921, **54**, 726.

(v) The production of pyridine derivatives from pyrrole has been discussed in Chapter XVII. Thus pyrrole with chloroform and sodium ethoxide gives β-chloropyridine; with methylene iodide pyridine itself is produced, while with benzalchloride, β-phenylpyridine is formed. Again, the N- or α-alkylpyrroles are converted at high temperatures into pyridines; thus N- or α-methylpyrrole gives pyridine and N-benzylpyrrole gives β-phenylpyridine. Acetylene combines with hydrogen cyanide at 800–950°, or with ammonia at 300° in presence of a catalyst, to give small yields of pyridine.

(vi) α- and γ-hydroxy-pyridines (α- and γ-pyridones) result from the action of ammonia on the corresponding α- and γ-pyrones, the oxygen of the ring being replaced by the imino group.

$$OC\begin{array}{c} CH=C{-}CH_3 \\ \\ CH=C{-}CH_3 \end{array}O + NH_3 \longrightarrow OC\begin{array}{c} CH=C{-}CH_3 \\ \\ CH=C{-}CH_3 \end{array}NH + H_2O$$

α,α'-Dihydroxy-pyridines are closely related to the imides of the corresponding dibasic aliphatic acids, and may be obtained from various derivatives of these acids. For instance, citrazinic acid results when citramide is warmed with sulphuric acid:

$$NH_2 \cdot CO \cdot C \cdot OH \begin{array}{c} CH_2{-}CONH_2 \\ \\ CH_2{-}CONH_2 \end{array} \longrightarrow HO_2C \cdot C \begin{array}{c} CH{-}C{-}OH \\ \\ CH=C{-}OH \end{array} N$$

Properties

The pyridine bases are stable colourless liquids with a characteristic and somewhat unpleasant smell. Pyridine itself is completely miscible with water and is very hygroscopic; it is dried with solid potassium hydroxide or barium oxide; sodium reacts with pyridine and cannot be used (see p. 536). The higher homologues are progressively less soluble in water and many are more soluble in cold water than in hot, a typical behaviour of tertiary amines (see p. 32). The pyridine bases boil undecomposed.

	Melting-point	Boiling-point
Pyridine	−42°	+115·3°
2-Methylpyridine (α-picoline) . . .	..	129°
3-Methylpyridine (β-picoline) . . .	..	143·5°
4-Methylpyridine (γ-picoline) . . .	..	143°
2,4-Dimethylpyridine ($\alpha\gamma$-lutidine) . .	..	159°
2,6-Dimethylpyridine ($\alpha\alpha'$-lutidine) . .	..	142·5°
2,4,6-Trimethylpyridine (collidine) . .	..	171°

Nearly all classes of organic compounds are soluble in pyridine, even many of high melting-point which scarcely dissolve in solvents such as

alcohol and benzene. It is consequently frequently used as a solvent. In addition, many salts dissolve in it to give conducting solutions, and it is extremely useful for inquiring into the electrolytic nature of compounds insoluble in water or attacked by water.

Pyridine is a tertiary amine and behaves as a weak mono-acidic base. Unlike pyrrole, it forms normal and fairly stable salts. It is frequently used in order to bring about reactions which involve the separation of hydrochloric or hydrobromic acids, the reaction being sometimes carried out in pyridine solution. Thus it is used in benzoylation; benzoyl chloride is dissolved in pyridine (which causes evolution of heat owing to the formation of an additive compound), and the amine, phenol, or alcohol is added. Again, pyridine (or quinoline) will remove hydrobromic acid, for example, from bromosuccinic ester, and this has the advantage over the use of alkali that the ester group is not saponified. Pyridine forms an efficient carrier in the chlorination and bromination of aromatic hydrocarbons, and it also acts as a catalyst, as does quinoline, in promoting the formation of Grignard reagents.

The salts of pyridine are almost all freely soluble in water, with the exception of the mercurichloride, $C_5H_5N,HCl,HgCl_2$, the chloroplatinate, $(C_5H_5NH)_2PtCl_6$, and the chloroaurate, $(C_5H_5NH)AuCl_4$. Similar compounds are formed by the homologues of pyridine, and the mercurichlorides are sometimes used for their separation and purification. Pyridine, like ammonia, combines readily with certain metals, notably those of the transitional groups of the Periodic Table and metals that are close to those groups, to give stable co-ordination complexes. An enormous variety of such complexes are known and the study of the pyridine complexes has been of importance in the development of the theory of co-ordination and of the stereochemistry of the metals.

Pyridine and its derivatives exhibit full aromatic character. Pyridine resembles benzene in not being oxidized by chromic acid or fuming nitric acid, and is even scarcely attacked by boiling with potassium permanganate. As in the benzene series, the homologues of pyridine are oxidized by potassium permanganate, the side-chains being degraded to nuclear carboxyl groups, whatever their length. The pyridine nucleus is even more stable towards oxidation than that of benzene, as is shown by the fact that when the phenylpyridines are oxidized, the benzene and not the pyridine nucleus is destroyed, the product being a pyridine-carboxylic acid. Pyridine itself possesses the useful property of dissolving potassium permanganate, and it may, therefore, be conveniently used as a solvent when oxidizing organic compounds with this reagent. Substitution takes place in the pyridine nucleus far less readily than with benzene. In this respect, and in many other ways, pyridine bears a much closer resemblance to nitrobenzene than to benzene. Thus, for example, the halogen atoms in the 2- or 4-chloro- (or bromo-) pyridines are not inert like the chlorine atom in chlorobenzene, but will react with amines and other reagents. Again, a methyl group in the 2 or 4 position is reactive enough to condense with

aldehydes. This behaviour is parallel with the reactivity of the chlorine atom in o- and p-chloronitrobenzene and of the methyl group in o- and p-nitrotoluene. A further point is that neither pyridine and its derivatives nor nitrobenzene react with acyl or alkyl halides in the presence of aluminium chloride (the Friedel-Crafts reaction). These resemblances are not mere coincidence, but arise from the similar electronic disturbances which are possible in pyridine and nitrobenzene and which can be indicated as follows:

Pyridine and its derivatives behave as tertiary amines in showing reactions characteristic of the unshared pair of electrons of the nitrogen atom. Of these the salt formation has been mentioned already. Pyridine is oxidized by perbenzoic acid in benzene solution to the N-oxide (I),[1] a water-soluble basic solid (melting-point 66°) which shows all the properties of a normal amine oxide (see p. 166).

Pyridine forms quaternary ammonium salts of various types. With dimethyl sulphate and with methyl iodide addition takes place with evolution of heat and formation of the 'methosulphate' (II) and methiodide, respectively. With the higher alkyl halides the quaternary salts are not formed with such ease and the mixture of pyridine and alkyl halide must be heated for several hours. Quaternary compounds are also formed with acid chlorides, such as benzoyl chloride; these are somewhat unstable compounds much more readily decomposed than the alkyl derivatives; their use as acylating agents has been mentioned above. With chloracetic acid pyridine gives the hydrochloride of pyridine-betaine (III), which can be obtained from the salt by the action of silver oxide. The properties of this betaine resemble those of the other members of the class (see p. 123); its zwitterion structure is shown by the fact that it is a hygroscopic compound, soluble in water, but insoluble in ether.

The quaternary salts of pyridine, such as N-methylpyridinium iodide (IV) are solids, mostly freely soluble in water and hygroscopic, which behave as strong electrolytes in solution. They differ in some respects,

[1] J. Meisenheimer, Ber. 1926, 59, 1848.

however, from their aliphatic analogues. Thus on heating to about 300°
in a sealed tube, the alkyl group 'migrates' partly to the α and partly to
the γ position in the ring to give a mixture of two substituted pyridines.

The reaction is not of much use for preparative purposes, but takes place
with better yield and at a lower temperature in the presence of certain
catalysts, such as copper bronze.[1] The reaction is similar to the Hofmann
'migration' which occurs on heating the hydrochlorides of secondary
aromatic amines (p. 78): since in the latter case the reaction appears to
involve the dissociation into an amine and an alkyl chloride followed by a
dimolecular reaction between the two, the formation of substituted pyri-
dines from pyridinium salts is almost certainly not a true migration, but
the dissociation of the pyridinium salt into its components followed by
bimolecular nuclear substitution. That substitution should take place in
the α and γ positions, while at room temperature the β position seems
the most reactive, probably arises from the profound influence of tem-
perature on orientation in the pyridine nucleus which is discussed later
(p. 527).

The quaternary hydroxides derived both from pyridine and its homo-
logues and condensed pyridine systems, such as quinoline (p. 549) and
acridine (p. 569), show exceptionally interesting properties which it will
be convenient to discuss together at this point. An aliphatic quaternary
hydroxide is a comparatively stable substance, and decomposes on heating
usually with the formation of an ethylenic compound (see p. 28). The
quaternary hydroxides of the aromatic cyclic bases do not undergo this
Hofmann degradation on heating, but many of them change rapidly at
room temperature into an isomeric substance which is a tertiary amine and
a non-electrolyte. The chemical nature of the isomer depends on the
substituents attached to the heterocyclic ring. There are two main possi-
bilities. The first is the formation of a pseudo-base; the hydroxyl ion
becomes covalently attached to the aromatic nucleus and by a rearrange-
ment of valencies the nitrogen atom becomes trivalent, the ring losing its
aromatic system of conjugated double bonds.

[1] A. Tschitschibabin and P. Rjumschin, *Zent.* 1916, ii, 146.

The structure of the pseudo-base was established by H. Decker,[1] who found that it could be oxidized, best by alkaline ferricyanide or by electrolytic oxidation, to the pyridone (V) (see p. 531), a characteristic reaction of a secondary alcohol. The conversion of the ammonium hydroxide into the pseudo-base (carbinol-base or cyclaminol) is not necessarily complete; often a tautomeric equilibrium is set up between the two species. The carbinol-bases are not stable compounds, which is hardly surprising in view of the fact that they are internal aldehyde-ammonias, derived from amino-aldehydes such as (VI).

| VI. | VII. | VIII. |

They show the curious property of reacting readily with an alcohol, such as ethyl alcohol, to give the ether (VII); this often takes place when an attempt is made to recrystallize the carbinol from alcohol. In some cases the pseudo-base itself is not formed, but the ether (VIII) which would be derived from two molecules of the pseudo-base by loss of water. The isomeric change is reversed if the pseudo-base or the anhydride is treated with a mineral acid, the product being the salt of the true quaternary ammonium base. The tautomerism between the ammonium compound and the pseudo-basic form is not restricted to the hydroxide; it occurs in other cases when the ammonium ion is brought into a solution which contains the anion of a very weak acid. Thus the cyclic quaternary ammonium cyanides (HCN being a very weak acid) tend to isomerize into compounds in which the cyano group is covalently linked to a carbon atom of the ring (see p. 553).

The second main possibility is the formation of an anhydro-base, that is a compound formed by loss of water from the true quaternary hydroxide. The simplest example of an anhydro-base is ammonia itself, since ammonium hydroxide, $[NH_4]OH$, loses water to form the anhydro-base NH_3. With the cyclic compounds this possibility arises when a methyl or methylene group is attached in the α or γ position to the aromatic ring. In these cases loss of water can take place to give an anhydro-base (sometimes called a methylene base) of structure (IX) or (X).

IX.

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[1] *Ber.* 1892, **25**, 443.

X.   XI.

The anhydro-bases, like the pseudo-bases, are converted by a mineral acid into the true quaternary salt by a process of addition. The methylene bases are of importance in connexion with the reactivity of methyl groups attached to heterocyclic nuclei and will be discussed later. Both the pseudo-bases and the anhydro-bases are, of course, not true pyridines, but are substitution products of dihydro-pyridines, such as (XI). Pseudo-base and anhydro-base formation are not restricted to pyridine derivatives, but occur in many other compounds; similar changes occur in oxonium bases, as in the pyrylium series.

In the case of the quaternary hydroxides derived from pyridine itself anhydro-base formation is impossible, and the equilibrium between the true ammonium hydroxide and the pseudo-base (XII) lies very much on the side of the former.

XII.   XIII.

Solutions obtained by adding alkali to solutions of the quaternary iodide do not show the decrease in conductivity with time which would accompany the isomeric change of an electrolyte into a covalently linked compound (XII).[1] On the other hand, the pseudo-base seems to be present in small concentration in the solution because oxidation with alkaline ferricyanide gives N-methyl-α-pyridone (XIII). The position of tautomeric equilibrium is probably largely determined by the fact that the ammonium base is stabilized by the conjugation of the double bonds in the true aromatic nucleus which it contains. If this conjugation is absent, as in the dihydropyrazine (XIV), the ammonium base changes completely into the pseudo-base (XV), which is sparingly soluble in water and can be isolated. It behaves as an alcohol, evolving methane with methyl magnesium iodide and being associated in benzene solution but not in water.[2]

The quaternary salts, however, which are formed by pyridine homologues with a methyl or methylene group in the α or γ position are converted by alkalis into anhydro-bases. Thus from α-benzylpyridine

[1] A. Hantzsch and M. Kalb, *Ber.* 1899, **32**, 3116.
[2] J. G. Aston, *J. Amer. C. S.* 1930, **52**, 5254; 1931, **53**, 1448.

$$
\underset{\text{XIV.}}{\overset{\displaystyle \begin{array}{c} \text{N} \\ \text{CH} \quad \text{CMe}_2 \\ \text{CMe}_2 \quad \text{CH} \\ \text{N+} \\ \mid \; [\text{OH}]^- \\ \text{Me} \end{array}}{}}
\longrightarrow
\underset{\text{XV.}}{\overset{\displaystyle \begin{array}{c} \text{N} \\ \text{CH} \quad \text{CMe}_2 \\ \text{CMe}_2 \quad \text{CHOH} \\ \text{N} \\ \mid \\ \text{Me} \end{array}}{}}
\qquad
\underset{\text{XVI.}}{\overset{\displaystyle \begin{array}{c} \\ \text{N} =\text{CH}\cdot\phi \\ \mid \\ \text{Me} \end{array}}{}}
$$

methiodide the anhydro base (XVI) is obtained. It is a yellow oil which is insoluble in concentrated aqueous potash, and decomposes on distillation.

The action of alkalis on certain of the quaternary derivatives of pyridine gives neither pseudo-base nor anhydro-base, but leads to opening of the ring. 2;4-Dinitrochlorobenzene contains a chlorine atom which is made sufficiently reactive by the nitro groups for a quaternary chloride to be formed with pyridine; if the resulting pyridinium chloride is treated with alkali, a derivative of glutaconic aldehyde is obtained.

$$ C_5H_5N\cdot C_6H_3(NO_2)_2[OH] \longrightarrow CHO\cdot CH:CH\cdot CH:CH\cdot NH\cdot C_6H_3(NO_2)_2 $$

Glutaconic aldehyde itself is formed by the action of alkali on the addition product which pyridine forms with three molecules of sodium bisulphite.

Substituted Pyridines

Halogen Derivatives. Pyridine is readily attacked by chlorine under a variety of conditions at ordinary temperature, and several chlorinated pyridines, substituted in the α, β, and γ positions, have been isolated from the products. The reaction cannot, however, be used for the preparation of simple chloro-pyridines of known orientation. In the case of homologues of pyridine the side chain may be attacked. The action of bromine on pyridine in the cold gives, according to the conditions, brominated pyridines or 4-pyridylpyridinium bromide hydrobromide, $C_5H_5N\cdot C_5H_4NH[Br]_2$,[1] the chlorine analogue of which is prepared by the action of thionyl chloride upon pyridine.[2] These complexes are hydrolysed by water at 150° to one molecule each of pyridine and γ-pyridone, thus giving a very convenient method for the preparation of the latter compound.

At high temperatures pyridine can be halogenated in presence of charcoal or pumice.[3] Chlorination at 250° gives a mixture which contains the 2-chloro compound, the 2,6- and 3,5-dichloro compounds, and the pentachloro compound. The positions taken by the entering chlorine atoms are at first sight somewhat surprising; it might have been expected that either the 2, 4, and 6 positions would have been occupied, or else the 3 and 5 positions, since in the vast majority of simple substitution reactions in benzene derivatives either ortho and para substitution predominates or else meta substitution. The reasons why chlorine attacks both sets of posi-

[1] See *Fried.* 1934, **21**, 523, 525.
[2] E. Koenigs and H. Greiner, *Ber.* 1931, **64**, 1049.
[3] H. J. den Hertog, jr., and J. P. Wibaut, *Rec. trav. chim.* 1932, **51**, 381, 940.

tions and not only one are shown by the products obtained when pyridine is brominated, a process which takes place more easily than chlorination. If pyridine and bromine are passed as vapour over the catalyst at 300° a mixture of 3-bromo and 3,5-dibromopyridine is formed in about half of the theoretical yield. At 500°, however, the reaction takes place much more readily and the product consists of 2-bromo and 2,6-dibromopyridine in 80 per cent. of the theoretical yield. At the intermediate temperature, 400°, both the 3,5- and 2,6-dibromopyridine are formed. In the benzene series a similar effect of temperature on the position taken up by the entering group has been observed in the bromination of bromobenzene[1] in presence of ferric bromide; the percentages of the three dibromobenzenes formed at different temperatures are as follows:

	Ortho	Meta	Para
55°	13·4	1·9	84·6
400°	20	23	57
500°	20·9	55·7	23·4
630°	18·9	59·9	21·2

2-Bromopyridine can be prepared by direct halogenation at 500°, but the corresponding chlorine compound is usually obtained by the action of phosphorus pentachloride on N-methyl-α-pyridone which is formed in the oxidation of N-methyl-pyridinium hydroxide (see pp. 525 and 531). The ketonic oxygen is replaced by two chlorine atoms and methyl chloride is eliminated.

The 3-halogenated pyridines are somewhat difficult to obtain. They can be prepared from potassium pyrrole and chloroform or bromoform (see p. 486) and also by the Sandmeyer reaction from the 3-amino-pyridines which can be diazotized (see p. 529). 4-Chloropyridine is obtained by heating 4-hydroxy-pyridine (γ-pyridone, see p. 531) in a sealed tube with phosphorus trichloride.[2]

As has been mentioned above, halogen atoms in the 2 or 4 positions are reactive, while those in the 3 position are not. 2-Chloropyridine reacts readily with ammonia and amines, just like an aliphatic chloro compound; in 3-chloropyridine, on the other hand, the chlorine atom resembles that in chlorobenzene. The chloropyridines are liquids with an odour like that of pyridine: they are fairly soluble in water and are volatile in steam.

[1] J. P. Wibaut, L. M. F. van Lande, and G. Wallach, *Rec. trav. chim.* 1933, **52,** 794.

[2] See R. Robinson and S. Thornley, *J.C.S.* 1924, **125,** 2170.

Nitro Derivatives. The nitropyridines are difficult to prepare and consequently have none of the importance for preparative purposes of the nitro compounds of the benzene series. Pyridine itself is only attacked by nitrating agents at a high temperature; if it is heated in fuming sulphuric acid to 330° and potassium nitrate added slowly, 3-nitropyridine is formed[1] and the yield is better in the presence of a little metallic iron.[2] At somewhat higher temperatures (370–450°) the yield of the 3-nitro compound decreases and 2-nitropyridine is formed in small quantity,[3] a phenomenon similar to that found in the bromination. The 2-nitro and 4-nitro compounds were unknown for many years, but can be obtained by the oxidation of the corresponding amino-pyridines with hydrogen peroxide in sulphuric acid.[4] If the pyridine nucleus already contains an amino or hydroxyl group, nitration takes place very much more easily; it is those groups also which facilitate nitration in the benzene nucleus. The nitropyridines are low-melting basic solids, not very soluble in water. They behave on reduction very much like the nitrobenzenes, giving azoxy and azo compounds with alkaline reagents and hydroxylamines and amines with neutral and acid reagents.

Amino Derivatives. Amino-pyridines are seldom prepared by reduction of the nitro compounds. The α- and γ-amino-pyridines are prepared from the corresponding chloro compounds by the action of ammonia, and all three mono-amines can be obtained from the amides of the mono-carboxylic acids either by the Hofmann reaction or by that of Curtius. α-Aminopyridine is most readily prepared by the action of sodamide on pyridine in toluene solution;[5] this reaction, leading to substitution in the α position, should be contrasted with the nitration which gives β-substitution. Pyridine behaves like nitrobenzene,[6] in which the meta position is reactive towards kationoid reagents, such as nitric acid, but the anionoid reagents sodamide and potassium hydroxide attack the ortho position.

The α- and γ-amino compounds differ from the β-amino derivatives in a fashion similar to that in the halogen-substituted pyridines. The β-amino-pyridines closely resemble the aromatic amines, and form diazonium salts and diazoamino compounds in the normal manner. The α- and γ-amino-pyridines, on the other hand, can only be diazotized with difficulty, as, for example, in concentrated nitric acid solution with nitrosyl sulphate, or in concentrated sulphuric acid; the diazonium compounds cannot be isolated, and the solutions when poured into water decompose into the hydroxy-pyridines and nitrogen. This behaviour may be connected with the fact that the α- and γ-amino-pyridines can react in a tautomeric imine form. The possibility of this tautomerism is indicated by the action of

[1] F. Friedl, *Ber.* 1912, **45**, 428.
[2] A. Kirpal and E. Reiter, ibid. 1925, **58**, 699.
[3] H. J. den Hertog, jr., and J. Overhoff, *Rec. trav. chim.* 1930, **49**, 552.
[4] A. Kirpal and W. Böhm, *Ber.* 1932, **65**, 680.
[5] A. E. Tschitschibabin and O. Seide, *J. Russ. Phys. Chem. Soc.* 1914, **46**, 1216.
[6] See W. Bradley and R. Robinson, *J.C.S.* 1932, 1254.

α-amino-pyridine with, for example, malonic ester, when a cyclic compound is produced:[1]

Sulphonic Acids. Pyridine is attacked by hot, fuming sulphuric acid with the formation of pyridine-β-sulphonic acid. This acid resembles benzene sulphonic acid; fusion with alkali gives β-hydroxy-pyridine, and fusion with potassium cyanide gives β-cyano-pyridine. The α- and γ-sulphonic acids are available by oxidation of the corresponding mercaptans, themselves prepared by the action of potassium hydrogen sulphide on the α- and γ-halogen pyridines. The pyridine sulphonic acids have a high melting-point and behave as internal salts (zwitterions); they are soluble in water and alcohol, but do not dissolve in ether or benzene. Their structure is best represented by a formula such as the following:

Hydroxy Derivatives. The hydroxy-pyridines behave both as weak acids and weak bases. They may be obtained by several methods, of which the more important are: (1) by fusing the sulphonic acids with alkali; (2) through the amino-pyridines by diazotization; with the β-amino-pyridine the reaction proceeds normally and the solution of the diazonium salt requires heating; with the α- and γ-amino-pyridines the conditions are different and have been described above; (3) from the hydroxy-pyridine carboxylic acids by elimination of the carboxyl group; for example, acetone and oxalic ester are condensed together to give acetone dioxalic ester; ring closure with acids gives chelidonic acid, converted by ammonia into chelidamic acid, which at 230° loses carbon dioxide to give γ-hydroxy-pyridine or γ-pyridone:

[1] A. E. Tschitschibabin, *Ber.* 1924, **57**, 1168.

(4) from the simple α- and γ-pyrones by the action of ammonia, as in the preceding method; (5) the hydroxyl group can be introduced directly into pyridine by passing pyridine vapour over dry caustic potash at 300–320°.[1] Hydrogen is evolved and the potassium salt of α-hydroxy-pyridine formed:

$$C_5H_5N + KOH \longrightarrow H_2 + C_5H_4N \cdot OK.$$

This is the attack of an anionoid reagent and resembles the action of sodamide which is discussed above.

As in the case of the chloro and amino derivatives, there is a marked difference in the behaviour of α- and γ-hydroxy-pyridines on the one hand and the β-hydroxy-pyridines on the other. β-Hydroxy-pyridine, a solid (melting-point 129°) easily soluble in water, is a true phenol; its absorption spectrum shows the characteristics of both a phenol and a pyridine,[2] and its refractivity is similar to that of its O-alkyl derivatives which are easily obtained from it by the action of either an alkyl bromide or diazomethane.[3] Its structure must be represented by formula (XVII).

XVII.	XVIII.	XIX.	XX.	XXI.

On the other hand, the question of the structure of α- and γ-hydroxy-pyridines is not so simple. Both substances are solids (α-compound, melting-point 107°; γ-compound, melting-point 148°) soluble in alcohol and water, but the γ-compound is very sparingly soluble in benzene and ether and forms a monohydrate. With diazomethane both give methyl ethers in which the methyl group is attached to oxygen: this is shown by the fact that the ethers can be demethylated with strong hydriodic acid and are basic compounds; further the same ethers can be obtained by the action of sodium methoxide on the α- and γ-chloropyridines; the structure of these ethers must be (XVIII) and (XIX). If heated with methyl iodide, however, they give isomeric ethers in which the methyl group is attached to nitrogen; this is known because the same compound is obtained both by the action of methyl iodide on α-hydroxy-pyridine and by oxidation in alkaline solution of pyridine methiodide, which is clearly an N-methyl compound. The N-ethers were originally allotted structures (XX) and ·(XXI), in which the aromatic conjugated system of three double bonds has disappeared, and, in consequence, are often known as N-methyl-α-pyridone and γ-pyridone, respectively. This view, however, entails several difficulties. The N-ethers show practically no ketonic reactions: they do not combine with phenylhydrazine, nor do they react as ketones with

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[1] Idem, ibid. 1923, **56**, 1879.

[2] F. Baker and E. C. C. Baly, *J.C.S.* 1907, **91**, 1127.

[3] K. v. Auwers, *Ber.* 1930, **63**, 2115.

Grignard reagents. With the latter an addition complex is formed, but it is decomposed by water with regeneration of the N-methyl-pyridone. Equally they do not behave as tertiary amines; they only unite with methyl iodide with difficulty and do not form true methiodides.[1] Further, the ketonic formulae imply that an aromatic structure is absent and that the compounds are derivatives of dihydropyridines, but the ultra-violet absorption spectrum of the compounds shows the selective absorption characteristic of aromatic compounds.[2] The only alternative formula in which the aromatic structure is retained is the 'zwitterion' structure[3]

XXII.   XXIII.

(XXII); the N-ethers can hardly be betaines, because they are liquids boiling without decomposition, but they may be resonance-hybrids of the pyridone (XXI) and the zwitterion (XXII).[4] A compound of this type, 3-cyano-4-methoxy-1-methyl-α-pyridone (XXIII), occurs in nature as the alkaloid ricinine.[5]

The structure of the α- and γ-hydroxy-pyridines themselves remains for discussion. The alternative formulae are the true phenol (e.g. XXIV), the pyridone (e.g. XXV), and the zwitterion (e.g. XXVI).

XXIV.   XXV.   XXVI.

The compounds may be tautomeric mixtures of phenol and pyridone, differing in the position of a hydrogen atom, or resonance-hybrids of the pyridone and zwitterion which only differ in electron distribution. There is very little evidence for the existence of the true phenolic structure (XXIV). α-Hydroxy-pyridine resembles its N-methyl ether (XX) in its refractivity and differs considerably from its O-methyl ether (XVIII) and from the phenolic β-hydroxy-pyridine (XVII).[6] None of the properties of the compounds suggest a true tautomerism such as that of the keto and enol forms of acetoacetic ester. The pyridone structure alone is unsatis-

[1] W. Borsche and I. Bonacker, *Ber.* 1921, **54**, 2679.
[2] E. R. Riegel and M. C. Reinhard, *J. Amer. C. S.* 1926, **48**, 1334.
[3] A. P. Smirnoff, *Helv. Chim. Acta*, 1921, **4**, 599.
[4] F. Arndt and A. Kalischek, *Ber.* 1930, **63**, 587.
[5] E. Späth and G. Koller, ibid. 1923, **56**, 880, 2454.
[6] K. v. Auwers, ibid. 1930, **63**, 2115.

factory for reasons which are similar to those given in the case of the N-alkyl compounds; the pyridones show an aromatic absorption in the ultra-violet, and few of their reactions are characteristic of a carbonyl group. Hence the most probable solution of the problem seems to be that, like their N-ethers, they are resonance-hybrids between the pyridone and the zwitterion structures (XXV and XXVI).[1]

Carboxylic Acids. The pyridine carboxylic acids may be prepared by some of the synthetical methods already described, and by the oxidation of pyridine homologues. Compounds containing condensed pyridine rings such as quinoline, isoquinoline, and their derivatives, yield pyridine carboxylic acids on oxidation, and these acids are therefore found as oxidative degradation products of many alkaloids.

The pyridine monocarboxylic acids are both basic and acidic, but the dicarboxylic and polycarboxylic acids show no basic properties. The α-carboxylic acids are decarboxylated very easily by heating with hydrochloric acid; the β- and γ-acids are more stable and lose their carboxyl group only by heating with lime. The α-carboxylic acids alone give a reddish colour with ferrous sulphate. This is Skraup's test for α-carboxylic acids in the pyridine and quinoline series; the structure of the red ferrous salts is unknown, but they are non-electrolytes and so the metal must be attached not only to the carboxyl group, but also by a co-ordinate link to the nitrogen atom.[2] In the β- and γ-acids the space-arrangement of the molecule makes such a double attachment of one molecule of the acid with a metal impossible, and these ferrous complexes are not formed. The physical properties of the pyridine carboxylic acids have many resemblances to those of the aliphatic amino-acids (see Chap. IV), which is not surprising in view of the fact that they contain a carboxyl group and a basic nitrogen atom. They have high melting-points and are insoluble or only very sparingly soluble in solvents such as ether and benzene. They probably have a 'zwitterion' structure similar to that of the aliphatic amino-acids.

		Melting-point
Pyridine α-carboxylic acid.	Picolinic acid	137°
Pyridine β-carboxylic acid.	Nicotinic acid	229°
Pyridine γ-carboxylic acid.	Isonicotinic acid	299°
Pyridine $\alpha\beta$-dicarboxylic acid.	Quinolinic acid	231°
Pyridine $\alpha\gamma$-dicarboxylic acid.	Lutidinic acid	239°
Pyridine $\alpha\beta'$-dicarboxylic acid.	Isocinchomeronic acid . . .	236°
Pyridine $\beta\gamma$-dicarboxylic acid.	Cinchomeronic acid . . .	259°
Pyridine $\beta\beta'$-dicarboxylic acid.	Dinicotinic acid . . .	323°

The pyridine carboxylic acids form the usual derivatives, esters, amides, acid chlorides, &c. The acid chlorides obtained by the action of thionyl chloride on the acids were long regarded as possessing abnormal structures, since the crude substances readily passed into high-melting products regarded as polymers. The acid chlorides are, however, quite normal; but

[1] F. Arndt and A. Kalischek, ibid. 1930, 63, 587; F. Arndt, ibid. 2963.
[2] H. Ley, C. Schwarte, and O. Münnich, ibid. 1924, 57, 349

in their preparation nuclear chlorination may occur, and if they contain a trace of thionyl chloride and are kept *in vacuo* over potassium hydroxide they slowly change to the hydrochloride of the acid chloride and finally the hydrochloride of the acid, thus giving products of high melting-point.[1]

The pyridine carboxylic acids are important reference substances in the orientation of pyridine derivatives. The α-, β-, and γ-carboxylic acids are called picolinic, nicotinic, and isonicotinic acids, respectively. The simplest proof of their orientation rests on the structures of quinoline and isoquinoline which are established by synthesis. Oxidation of quinoline (I) gives quinolinic acid (II), which must be pyridine $\alpha\beta$-dicarboxylic acid, and, when heated, this acid yields nicotinic acid by loss of a molecule of carbon dioxide. Consequently nicotinic acid must be either pyridine α- or β-carboxylic acid. Similarly isoquinoline (IV) on oxidation yields cinchomeronic acid (V), which must therefore be pyridine $\beta\gamma$-dicarboxylic acid. When heated cinchomeronic acid loses carbon dioxide to give a mixture of nicotinic acid and isonicotinic acid. Nicotinic acid must, therefore, be the β-acid, isonicotinic acid must be the γ-acid (VI), and the remaining picolinic acid must be the α-carboxylic acid.

Pyridine Homologues. The three isomeric monomethylpyridines are known as α-, β-, and γ-picoline, respectively. The isomeric dimethylpyridines are known as the lutidines, whilst the trimethylpyridines are referred to as the collidines. In general behaviour the alkylpyridines resemble pyridine itself, and only those properties which are associated with the alkyl groups need be considered. The oxidation of the alkyl groups to carboxyl has already been mentioned, but the most interesting property of the alkylpyridines and their derivatives is that a methyl group in the α or γ position is reactive. For example on heating α-picoline with benzaldehyde and a little zinc chloride, a benzylidene derivative (VII) is obtained, and with chloral an aldol type of compound (VIII) is produced.

[1] See H. Meyer and R. Graf, *Ber.* 1928, **61**, 2202.

This reactivity is connected with the fact that the α- and γ-methyl-pyridines appear to react in a tautomeric methylene form. This behaviour, which is also shown in the methyl-quinolines and isoquinolines is discussed in detail later (p. 554).

Polypyridyls. Compounds containing two pyridine nuclei joined together can be obtained directly from pyridine in two ways. If pyridine vapour is passed through a hot tube, a product is obtained from which

αα′-Dipyridyl   αγ′-Dipyridyl   αβ′-Dipyridyl   γγ′-Dipyridyl

three dipyridyls can be isolated, the αα′-, αγ′-, and αβ′-compounds.[1] Of these compounds the first (melting-point 69°) has a special interest; because of the space-arrangement of the two nitrogen atoms, it forms chelate co-ordination complexes of great stability with certain metals, especially those in or near to the transitional triads of the Periodic Table. In these complexes the two nitrogen atoms are attached to the metal by co-ordinate links, so that a ring is formed, and the structure of the kation of the ferrous compound [Fe dipy$_3$]Br$_2$,6H$_2$O (dipy = 1 mol. of αα′-dipyridyl) can be indicated by the formula:

The arrangement of the nitrogen atoms is, however, not planar but octahedral, as has been proved by the resolution of this compound into optically active forms.[2] The complex with the ferrous ion is very characteristic; quite dilute solutions of the dipyridyl and of ferrous sulphate give an intense pink colour when mixed, which can be used as a test for the presence of either substance. It is possibly owing to the stability and ease of formation of this complex that if pyridine is heated with dry ferric chloride in an autoclave to 340°, considerable quantities of αα′-dipyridyl are formed.[3] In addition to this dipyridyl, four other dipyridyls are formed in

[1] H. Meyer and A. Hoffmann-Meyer, *J. pr. Chem.* 1921, **102**, 287.

[2] A. Werner, *Ber.* 1912, **45**, 434.

[3] F. Hein and W. Retter, ibid. 1928, **61**, 1790; G. T. Morgan and F. H. Burstall, *J.C.S.* 1932, 20.

smaller amount; there are six possible dipyridyls and all have been identified by Morgan and Burstall in the product of this reaction with the exception of the $\gamma\gamma'$-compound. Tripyridyls are also produced, notably the $\alpha\alpha\alpha$-tripyridyl, which forms co-ordination compounds with metals,

$\alpha\alpha\alpha$-Tripyridyl

all three nitrogen atoms combining with the metal. The study of these complexes has been of importance both for the stereochemistry of the metals and for analytical methods.[1]

The second reaction of pyridine which leads to dipyridyls is that with sodium.[2] If sodium and pyridine are left together at room temperature, air being excluded, a green solid is obtained, the analysis of which indicates that it is a complex of one atom of sodium and two molecules of pyridine: one molecule of pyridine seems to be attached only loosely and can be removed by distillation under reduced pressure; it can also be replaced by a molecule of another tertiary base. The solid is vigorously attacked by water and is spontaneously inflammable in air. If the oxidation is controlled, the decomposition products of the complex can be obtained, and contain dipyridyls and pyridylpiperidines, that is dipyridyls in which one ring has been completely reduced. The main product is $\gamma\gamma'$-dipyridyl (melting-point 112°), the isomer which has not been detected among the products of the pyrolysis of pyridine with ferric chloride; the $\alpha\alpha'$-, $\beta\beta'$-, and $\beta\gamma'$-dipyridyls can also be isolated. Of the products containing a reduced ring, β-pyridyl-α-piperidine is formed in the largest quantity. This compound, which contains an asymmetric carbon atom, is identical with the racemic form of the alkaloid anabasine which occurs in its laevo form in the Central Asian plant, *Anabasis aphylla*, and which, as an insecticide, is an article of commerce.[3]

Anabasine

Anabasine is isomeric with nicotine (p. 516) and resembles it in being a liquid soluble in water.[4] The sodium-pyridine complex is most probably a mixture, and its constitution is not known with certainty. It seems likely

[1] See G. T. Morgan and F. H. Burstall, *J.C.S.* 1934, 1498; G. T. Morgan, 'Recent Researches in the Chemistry of the Rarer Elements', ibid. 1935, 554.

[2] B. Emmert, *Ber.* 1914, **47**, 2598; 1916, **49**, 1060; 1917, **50**, 31; C. R. Smith, *J. Amer. C. S.* 1924, **46**, 414.

[3] C. R. Smith, ibid. 1931, **53**, 277; 1932, **54**, 397.

[4] A. Orekhov and G. Menschikov, *Ber.* 1931, **64**, 266; 1932, **65**, 232.

that the molecule contains two atoms of sodium and two molecules of pyridine and that the two latter are joined together. It may well be a mixture of the sodium derivatives of tetrahydrodipyridyls,[1] such as:

$$Na \cdot N \underset{CH=CH}{\overset{CH=CH}{<}} > CH-HC \underset{CH=CH}{\overset{CH=CH}{<}} > N \cdot Na.$$

The action of lithium on pyridine is similar to that of sodium, but potassium does not react so readily.

Piperidine and the Reduction Products of Pyridine

The nucleus of pyridine is reduced much more easily than that of benzene. Under a variety of conditions it takes up six atoms of hydrogen and forms the fully saturated substance piperidine. Piperidine is produced from pyridine by the action of sodium and alcohol (a reagent which will not reduce benzene), by electrolytic reduction, and catalytically by hydrogen and nickel or as the hydrochloride in absolute alcohol by hydrogen in presence of platinum oxide.

Vigorous reduction of pyridine with hydriodic acid at 300° leads to ammonia and n-pentane. Di- and tetrahydro derivatives of pyridine can, however, be prepared by the partial reduction of pyridine; while in the benzene series, with a few exceptions such as the dicarboxylic acids, it is difficult to obtain partially reduced compounds by direct reduction.

Dihydro-pyridines are obtained by reducing moist ethereal solutions of pyridine carboxylic esters with aluminium amalgam. Such dihydro-pyridines are either identical or isomeric with the 1,4-dihydro-pyridines produced by a number of synthetical reactions.[2] 1,4,1′,4′-Tetrahydro-4,4′-dipyridyls may also be obtained during the reduction. The dihydro-pyridines are easily oxidized by nitrous fumes or dilute nitric acid to the pyridines.

Tetrahydro-pyridines are produced in small quantity during the reduction of pyridine to piperidine with sodium and alcohol. They are readily isolated as their dibromides, from which they are regenerated by reduction with zinc dust and sulphuric acid. Such tetrahydro-pyridines are probably the Δ_3 derivatives (I), since they give normal N-acyl derivatives, and are not identical with synthetical Δ_2-tetrahydro-pyridines (II).

I. Δ_3 II. Δ_2 III.

These Δ_3-tetrahydro-pyridines are very difficult to reduce to piperidines, the reduction being possible only by the action of hydriodic acid and

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[1] See B. Emmert and R. Buchert, ibid. 1921, **54**, 204.

[2] O. Mumm and W. Beth, ibid. 1592.

phosphorus. The Δ_2 compounds are prepared by the action of ammonia on a δ-bromoketone (III); they are readily reduced with tin and hydrochloric acid, and on treatment with benzoyl chloride and alkali give the N-benzoyl derivative of the δ-amino-ketone.

Piperidine. Piperidine occurs in some quantity, probably as a simple salt, in the South African plant *Psilocaulon absimile*[1] and in traces in black pepper;[2] it is found in combination with piperic acid as the acid amide piperine, $CH_2O_2 : C_6H_3 \cdot CH : CH \cdot CH : CH \cdot CO \cdot N(C_5H_{10})$, which is the alkaloid of various kinds of pepper (see p. 136). Another well-known alkaloid containing the piperidine nucleus is coniine, the poisonous principle of hemlock (*Conium maculatum*), which is α-*n*-propylpiperidine. Coniine was the first alkaloid whose complete synthesis and resolution were carried out.[3]

In addition to the synthetical methods which have already been given, piperidine is obtained by the action of potassium hydroxide on 5-chloro- or -bromo-*n*-amylamine (see p. 468).

Piperidine is a colourless liquid, boiling-point 106°, miscible with water and most organic solvents. It has a powerful ammoniacal odour recalling that of the alkylamines, and fumes in the air; it turns red litmus blue and absorbs carbon dioxide from the air. It is a much stronger base than pyridine or ammonia; the apparent dissociation constants at 25° and their relative values are as follows:

	Pyridine.	*Ammonia.*	*Piperidine.*
k	$2 \cdot 28 \times 10^{-9}$	$1 \cdot 87 \times 10^{-5}$	$1 \cdot 58 \times 10^{-3}$
relative	1	8,000	700,000

In its general chemical properties it behaves like a typical aliphatic secondary amine. The NH group can be readily acetylated, benzoylated, and alkylated with alkyl halogen compounds, e.g. it combines violently with methyl iodide; it yields an N-nitroso compound with nitrous acid and piperidyl-urethane, $C_5H_{10}N \cdot CO_2Et$, by the action of chloroformic ester. The N-alkylpiperidines may be synthesized from 1,5-dihalogenpentanes and a primary amine.

The oxidation of piperidine leads to a variety of products depending on the oxidizing agent. Mention has already been made of the dehydrogenation of piperidine to pyridine by means of sulphuric acid, nitrobenzene, or silver acetate; it also occurs when the vapour of piperidine is passed over manganous oxide at 600°.[4] The action of hydrogen peroxide on piperidine leads to piperidine oxide, which is a hydroxylamine derivative, $C_5H_{10}N \cdot OH$. The N-alkyl-piperidines, like the tertiary aliphatic bases, give under these conditions normal amine oxides of the type

$$C_5H_{10}NMe \rightarrow O.$$

[1] C. Rimington, *S. African J. of Science*, 1934, **31**, 184.
[2] E. Späth and G. Englaender, *Ber.* 1935, **68**, 2218.
[3] A. Ladenburg, *Annalen*, 1888, **247**, 85.
[4] P. Sabatier and A. Fernandez, *C.r.* 1927, **185**, 241.

The unsubstituted piperidine ring is difficult to disrupt by oxidation, except by the action of potassium permanganate, which attacks it even in the cold with liberation of ammonia.[1] By long heating with chromic acid, β-amino-propionic acid has been obtained,[2] and γ-amino-butyric acid has been obtained by oxidation with nitric acid. The piperidine ring is broken down smoothly by oxidizing the N-benzoyl derivative with potassium permanganate, when 5-benzoylamino-n-valeric acid is produced.

$$H_2C \underset{CH_2-CH_2}{\overset{CH_2-CH_2}{\big<}} N \cdot CO\phi \longrightarrow \underset{CH_2-CO_2H}{\overset{CH_2-CH_2-NH \cdot CO\phi}{CH_2 \big<}}$$

The piperidine ring is broken down by the action of cyanogen bromide on the N-alkyl or aryl derivatives, a reaction which has been discussed above (p. 328), and also by heating the N-benzoyl compound with phosphorus pentachloride.[3] In this latter reaction the dichloro compound first formed is converted into an imino-chloride which loses benzonitrile to give 1,5-dichloropentane:

$$H_2C \underset{CH_2-CH_2}{\overset{CH_2-CH_2}{\big<}} N \cdot CO \cdot \phi$$

$$\longrightarrow \underset{CH_2-CH_2Cl}{\overset{CH_2-CH_2 \cdot N:CCl\phi}{CH_2 \big<}} \longrightarrow \underset{CH_2-CH_2Cl}{\overset{CH_2-CH_2Cl}{CH_2 \big<}} + \phi \cdot CN.$$

This is a convenient method for making this dichloropentane.

The exhaustive methylation of piperidine (see p. 28) ultimately leads to 1,3-pentadiene (piperylene), $CH_3 \cdot CH:CH \cdot CH:CH_2$, and not the 1,4 isomer (IV), which might be expected.

$$\underset{\underset{Me_2}{N}}{\overset{CH_2}{\underset{CH_2}{\big<} \, \underset{CH_2}{CH_2}}} [OH] \longrightarrow \underset{NMe_2}{\overset{CH_2}{\underset{CH_2}{CH} \, \underset{CH_2}{CH_2}}} \longrightarrow \underset{NMe_3 [OH]}{\overset{CH_2}{\underset{CH_2}{CH} \, \underset{CH_2}{CH_2}}} \longrightarrow \underset{Piperylene}{\overset{CH}{\underset{CH_2}{CH} \, \underset{CH_3}{CH}}}$$

$$\underset{CH_2}{\overset{CH_2}{CH} \, \underset{CH_2}{CH}}$$

1,4-Pentadiene   IV.

Similar cases in which a double bond migrates in this reaction are not uncommon; for example, exhaustive methylation of γ-phenylpropylamine, $\phi \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NH_2$, gives propenyl benzene, $\phi \cdot CH=CH \cdot CH_3$, and not allyl benzene, $\phi \cdot CH_2 \cdot CH:CH_2$.[4] The new double bond is formed during the decomposition in such a position as to produce a conjugated system of

[1] For the oxidation of piperidine with potassium permanganate in acetone see S. Goldschmidt and V. Voeth, *Annalen*, 1924, **435**, 265.

[2] P. Karrer and A. Widmer, *Helv. Chim. Acta*, 1926, **9**, 886.

[3] J. v. Braun, *Ber.* 1904, **37**, 2915.

[4] L. Senfter and J. Tafel, ibid. 1894, **27**, 2309; see W. Baker and R. Robinson, *J.C.S.* 1925, **127**, 1429.

double bonds. The phenomenon recalls the change of a $\beta\gamma$ unsaturated acid into its $\alpha\beta$ isomer, and of an allyl benzene into a propenyl benzene, such as eugenol into iso-eugenol.

The homologues of piperidine, i.e. the compounds in which one or more hydrogen atoms attached to carbon are replaced by alkyl groups, are usually prepared by the reduction of the corresponding pyridines. They are sometimes called by names which are derived from that of the pyridine by inserting -pe- after the first syllable; thus the methyl piperidines can be referred to as the pipecolines and the dimethylpiperidines as the lupetidines. Of the monoalkyl piperidines all the α- and β- compounds, but not the γ- compounds, necessarily contain an asymmetric carbon atom and can be resolved into optical antimers. Dialkyl piperidines with two similar alkyl groups attached to one carbon atom are inactive, but if they are attached to two different carbon atoms of the ring, there are two possibilities. An unsymmetrically substituted compound, such as 2,4-dimethylpiperidine, exists as two distinct racemic forms, each capable of resolution, while a symmetrical compound, such as 2,6-dimethylpiperidine, contains two similar centres of asymmetry and exists as one racemic form and one meso form.

Of the keto-piperidines or piperidones, the α-piperidones are merely the lactams (cyclic amides) of the δ-amino-carboxylic acids, but certain of the γ-piperidones are of considerable interest. When phorone (I) (prepared by the self-condensation of acetone) is treated with ammonia, the product is triacetonimine (II).

Phorone I.   NH II.   NH$_2$ III.   NH IV.

Diacetonamine (III) (prepared by the action of ammonia upon mesityl oxide) and acetaldehyde yield the closely allied product vinyldiacetonimine (IV). The similarity of (II) and (IV) to tropinone, which may be written as (V), is at once apparent. Tropinone is the ketone obtained by oxidizing the secondary alcohol tropine, and tropine is a cleavage product of most of the *Solanaceae* alkaloids, atropine, hyoscyamine, &c., and the same fundamental structure is found in the coca alkaloids, cocaine, &c.

Tropinone V.   Cocaine VI.

$$MeO_2C \cdot C \cdot O \cdot CO\phi$$

$$\begin{array}{cc} \dot{C}H_2 & \dot{C}H_2 \\ | & | \\ \dot{C}Me_2 & \dot{C}Me_2 \\ \multicolumn{2}{c}{\diagdown N \diagup} \\ \multicolumn{2}{c}{CH_3} \end{array}$$

Eucaine

VII.

$$CH \cdot O \cdot CO\phi$$

$$\begin{array}{cc} \dot{C}H_2 & \dot{C}H_2 \\ | & | \\ \dot{C}Me_2 & \dot{C}HMe \\ \multicolumn{2}{c}{\diagdown N \diagup} \\ \multicolumn{2}{c}{H} \end{array}$$

β-Eucaine

VIII.

Atropine is tropine in which the alcoholic group is esterified by *dl*-tropic acid, $\phi \cdot CH(CH_2OH) \cdot CO_2H$; *l*-cocaine, a very valuable local anaesthetic, is represented by (VI), and with this as model have been built up synthetical local anaesthetics such as eucaine (VII) and β-eucaine (VIII), which are readily prepared from triacetonimine and vinyldiacetonimine.

One remarkably simple synthesis of tropinone deserves fuller discussion. There is reason to believe that in the synthesis of atropine and cocaine in the cells of a living plant the first stage is the formation of tropinone which is converted by subsequent reactions into the various alkaloids of the atropine class.[1] Hence it is of peculiar interest to find a reaction in which tropinone is formed in good yield from simple starting materials which can occur as constituents of the cell and under conditions of temperature and acidity which are biologically possible. Robinson[2] showed that the esters or salts of acetone dicarboxylic acid condense with succindialdehyde and methylamine in alcoholic or aqueous solution at room temperature to give the ester or salt of tropinone dicarboxylic acid, and that this acid readily loses carbon dioxide to give tropinone.

$$\begin{array}{ccc} \diagup CH_2 \cdot CO_2Et & OCH \cdot CH_2 & \\ CO & H_2NMe & | \\ \diagdown CH_2 \cdot CO_2Et & OCH \cdot CH_2 & \end{array}$$

$$\xrightarrow{\hspace{1cm}} \begin{array}{c} CO_2Et \\ | \\ \diagup CH\!-\!CH\!-\!CH_2 \\ CO \quad\quad NMe \quad | \\ \diagdown CH\!-\!CH\!-\!CH_2 \\ | \\ CO_2Et \end{array} \xrightarrow{\hspace{1cm}} \begin{array}{c} \diagup CH_2\!-\!CH\!-\!CH_2 \\ CO \quad\quad NMe \quad | \\ \diagdown CH_2\!-\!CH\!-\!CH_2 \end{array}$$

Methylamine, acetone dicarboxylic acid, and succindialdehyde are possible cell constituents; the latter may well be formed from the amino-acid ornithine by deamination, decarboxylation, and oxidation.[3]

$$H_2N(CH_2)_3 \cdot CHNH_2 \cdot CO_2H$$
$$\xrightarrow{\hspace{1cm}} HO(CH_2)_3 \cdot CO \cdot CO_2H \xrightarrow{\hspace{1cm}} OCH \cdot CH_2 \cdot CH_2 \cdot CHO$$

In these experiments the presence of free methylamine makes the reaction mixture more alkaline than is possible in a living cell. Further investiga-

[1] R. Willstätter, *Ber.* 1900, **33**, 1160.   [2] R. Robinson, *J.C.S.* 1917, **111**, 762.
[3] See also R. C. Menzies and R. Robinson, ibid. 1924, **125**, 2163.

tion, however, has shown[1] that the salts of acetone dicarboxylic acid condense readily with methylamine and succindialdehyde in solutions in which the hydrogen-ion concentration is kept constant by a buffer to a value within the range known to prevail in plant cells. Under these conditions not only is the yield good (at pH $=$ 7 it is 70–75 per cent.: at pH $=$ 9, 60–70 per cent.), but the first product formed is tropinone and not its dicarboxylic acid, the latter losing carbon dioxide immediately it is formed. There is thus reason for believing that the fundamental reaction which leads to the natural synthesis of the tropinone alkaloids is known.

Another type of compound containing a bridged piperidine ring is quinuclidine:

$$
\begin{array}{c}
\diagup CH_2 \!\!-\!\!-\!\!- CH_2 \diagdown \\
CH\!-\!CH_2\!-\!CH_2\!-\!N \\
\diagdown CH_2 \!\!-\!\!-\!\!- CH_2 \diagup
\end{array}
$$

which has been prepared synthetically, and whose nucleus occurs in the important alkaloids quinine and cinchonine. It should be pointed out that, for steric reasons, rings fused to the meta and para positions of an aromatic nucleus (benzene, pyridine, &c.) are probably incapable of existence unless they contain at least ten members,[2] but such restrictions do not apply to reduced cyclic systems which are not planar, and in which substituents do not lie in the (average) plane of the ring.

QUINOLINE

Quinoline and isoquinoline are the two isomeric benzopyridines, and bear the same relation to pyridine that naphthalene does to benzene. Quinoline contains the benzene ring fused to the pyridine ring in the α and β positions, while in isoquinoline it is fused to the β and γ positions of the pyridine ring.

Quinoline   Isoquinoline

The positions of substituents in the two ring systems are usually indicated as shown. The number of isomers in substituted quinolines is very great; even a mono-substituted quinoline can exist in seven isomeric forms.

Quinoline occurs with pyridine in coal-tar, and was isolated in a crude state from this source by Runge in 1834. The quinoline of commerce is either obtained from coal-tar or prepared synthetically. It also occurs in bone oil and is produced by heating the quinoline alkaloid cinchonine with potassium hydroxide (C. Gerhardt, 1842). Quinine under the same circumstances yields 6-methoxyquinoline.

[1] C. Schöpf and G. Lehmann, *Annalen*, 1935, **518**, 1.
[2] See L. Ruzicka, J. B. Buijs, and M. Stoll, *Helv. Chim. Acta*, 1932, **15**, 1220, for an account of earlier work; also S. G. P. Plant, *J.C.S.* 1933, 1586.

The fundamental formula given above for quinoline is fully substantiated by the various quinoline syntheses, and by its chemical behaviour. There still remains the question of the disposition of the remaining valencies of the carbon and nitrogen atoms, a problem exactly analogous to that presented by the structure of naphthalene. As has already been pointed out in discussing the constitution of pyridine, the chemistry of benzene is most readily interpreted by attributing to it the Kekulé formula with the proviso that the structure is symmetrical and is a resonance-hybrid of the two possible Kekulé forms. With naphthalene the problem is more complicated because, although the physical evidence suggests that the states of linkage of those carbon atoms which are not members of both rings are all identical, yet many of the chemical reactions of naphthalene are more readily comprehensible if it is assumed that in the reactive state the double bonds are fixed so that each ring consists of a conjugated system, as in (I).[1] Similarly in quinoline (and isoquinoline) the chemical reactions, especially the reactivity of methyl substituents in certain positions which is discussed below, indicate that the hetero-ring may not be symmetrical, but may consist of alternate single and double bonds. If this evidence is accepted, and there is much to be said against it, quinoline must be either (II) or (III), and of these (II) is far more likely because each ring is a conjugated system of double bonds.

I.   II.   III.

Quinoline Syntheses

(i) The first synthesis of quinoline was due to W. Koenigs (1879), who passed the vapour of allylaniline over red-hot lead oxide:

(ii) Another early synthesis of quinoline was due to A. von Baeyer (1879). o-Nitrohydrocinnamic acid when reduced yields the lactam dihydrocarbostyril; this when treated with phosphorus pentachloride gives a dichloroquinoline which is reduced by hydriodic acid to quinoline.

[1] See L. F. Fieser and W. C. Lothrop, *J. Amer. C. S.* 1935, **57**, 1459.

(iii) A simple quinoline synthesis is due to V. Kulisch[1] who heated o-toluidine with glyoxal and concentrated sodium hydroxide to 150° and obtained quinoline in 35–40 per cent. yield:

$$\text{(structure: o-toluidine with CH}_3\text{ and NH}_2\text{)} \quad \begin{array}{c}\text{CHO}\\|\\\text{CHO}\end{array} \longrightarrow \text{(quinoline structure)} + 2\text{H}_2\text{O}.$$

(iv) *The Skraup Reaction.* This synthesis[2] is of very general application, and may be used for the preparation of a great variety of quinolines which are substituted in the benzene, as distinct from the pyridine, nucleus. The method consists in heating a primary aromatic amine with glycerol, concentrated sulphuric acid, and an oxidizing agent, the latter being usually nitrobenzene, but the use of arsenic acid gives a smoother and less violent reaction. The Skraup reaction frequently takes place with great violence, and a point of practical importance is to carry out the reaction under a long and wide reflux condenser which is sufficiently large to contain the whole contents of the reaction flask. In the case of the synthesis of quinoline itself from nitrobenzene, the reaction probably takes place through the following stages. The glycerol and sulphuric acid react together to give acrolein, $\text{CH}_2\!:\!\text{CH}\cdot\text{CHO}$, which condenses with one molecule of aniline and combines additively with a second, thus yielding the anil of β-anilinopropionic aldehyde. Loss of a molecule of aniline and ring closure then take place, followed by oxidation of the resulting dihydroquinoline.

$$\text{(structure with NH}_2\phi\text{, OCH, CH, CH}_2\text{, NH}_2\text{)} \longrightarrow \text{(structure with N}\phi\text{, CH, CH}_2\text{, CH}_2\text{, NH)}$$

$$\longrightarrow \phi\cdot\text{NH}_2 + \text{(structure CH=CH, CH}_2\text{, NH)} + \text{O} \longrightarrow \text{(quinoline structure CH=CH, CH, N=CH)} + \text{H}_2\text{O}$$
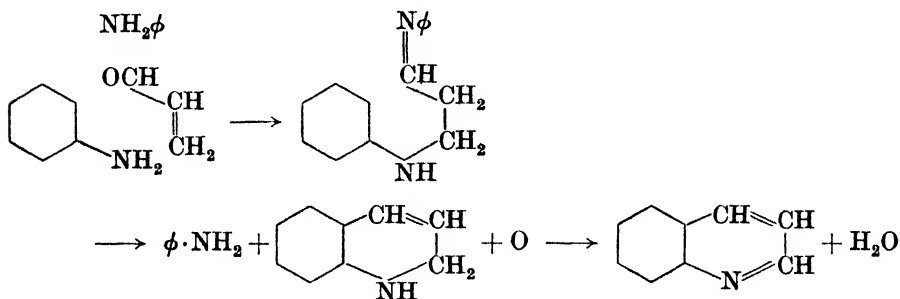
In this scheme it will be noted that the carbon atom of the aldehyde group becomes the γ-carbon atom of the quinoline nucleus, and not the alternative α-carbon atom. If, as was at one time supposed, the reaction proceeds by direct ring closure of the acrolein anil, followed by oxidation, then crotonic aldehyde should yield γ-methylquinoline. If, however, the nucleus of that aniline molecule which has combined additively with the double bond of the unsaturated aldehyde is the one which becomes the benzene nucleus of the quinoline molecule, then crotonic aldehyde should give α-methylquinoline, which is actually the case.

[1] *Sitz. Akad. Wiss. Wien*, 1894, **103**, ii b, 206; *Monats.* 1894, **15**, 276.

[2] Z. H. Skraup, ibid. 1880, **1**, 317.
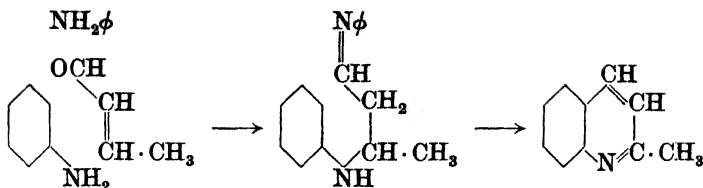
It therefore follows that a compound of the type of the anil of β-anilino-
n-butyric aldehyde can undergo ring closure in one direction only. The point
can be shown more clearly by writing the formula of the compound in the
two ways (IV) and (V).

IV.　　　　　　　　V.
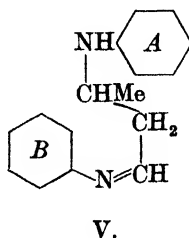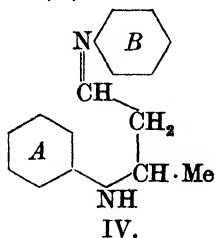
Ring closure takes place so that the phenyl ring marked A becomes part
of the quinoline structure, and not the phenyl ring marked B; in other words,
the stage before ring closure is that shown in (IV) and not that shown in
(V). This result is hardly surprising; the nucleus A is that of an alkyl-
aniline, and in such compounds the hydrogen atom in the ortho position
to the imino group is known to be reactive, while the nucleus B is that of
an anil, a class of compounds which are less reactive. A further point is
that ring closure with nucleus B would involve direct elimination of a
molecule of aniline, while ring closure with nucleus A can take place by
isomeric change to a saturated ring structure followed by loss of a mole-
cule of aniline, and this is a more probable mechanism.
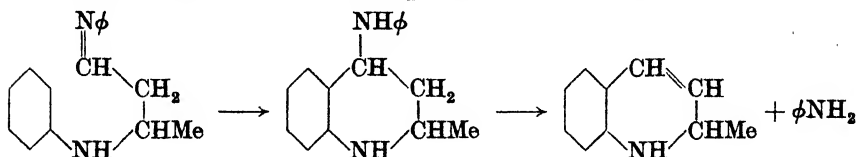
The Skraup synthesis is of exceedingly wide application, and almost
any aromatic amine will yield a quinoline; even dinitroaniline may be
employed. A m-substituted aniline may give a mixture of two isomeric
quinolines. Simple diamines react twice, giving the so-called phenanthro-
lines, e.g. (VI).

VI.　　　　　　　VII.　　　　　　　VIII.

N n
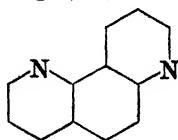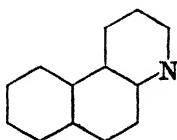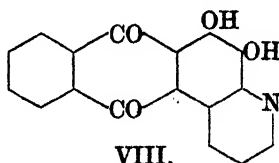
β-Naphthylamine gives only one product (VII), owing to the reactivity of the hydrogen atom in the α-position. In certain cases (e.g. preparation of alizarin blue (VIII) from β-nitroalizarin) the nitro compound alone may be employed with glycerol and sulphuric acid to give a quinoline, the nitro group being reduced during the reaction.

Of interest owing to its close resemblance to the Skraup synthesis is the production of quinoline in 50 per cent. of the theoretical yield by heating the anil of β-anilino-acrolein with zinc chloride.[1]
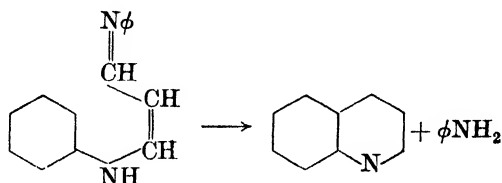
It may also be pointed out that the Skraup reaction bears a strong formal relationship to the production of indoles by heating a primary aromatic amine with an α-halogen ketone (see p. 497).

(v) The quinoline synthesis of O. Doebner and W. von Miller[2] is closely allied to the Skraup synthesis. It consists in acting upon a mixture of an aromatic amine and an aldehyde with hydrochloric acid or zinc chloride; in the case of aniline and acetaldehyde the product is α-methylquinoline (quinaldine). The yield of quinaldine is not high, and a variety of other bases, both secondary and tertiary, are formed at the same time. The mechanism of the reaction is not fully known, but the nature of the by-products throws a certain amount of light upon it.[3] In the presence of dilute hydrochloric acid acetaldehyde condenses with aromatic amines to give the so-called 'aldol bases' of W. von Miller and J. Plöchl:[4] these compounds are formed from a molecule of crotonaldehyde, $CH_3 \cdot CH : CH \cdot CHO$, the self-condensation product of acetaldehyde, and one molecule of amine, and are known to have the structure (IX).[5]

IX.   X.   XI.   XII.
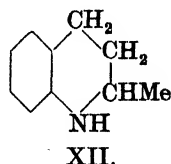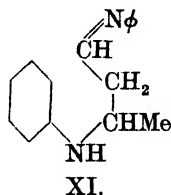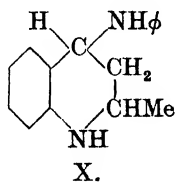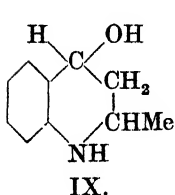
They condense with a further molecule of amine to give a compound which may either have the structure (X) or (XI), the latter being analogous to the intermediate in the Skraup synthesis. All these compounds are converted on heating with acids into quinaldine and its reduction product,

[1] W. König, *Ber.* 1923, **56**, 1853.   [2] Ibid. 1883, **16**, 2464.
[3] W. H. Mills, J. E. G. Harris, and H. Lambourne, *J.C.S.* 1921, **119**, 1294.
[4] *Ber.* 1896, **29**, 1462.
[5] M. G. Edwards, R. E. Garrod, and H. O. Jones, *J.C.S.* 1912, **101**, 1376.

tetrahydro-quinaldine (XII); the loss of water from (IX) or of aniline from (X) or (XI) would give dihydroquinaldine (XIII), and this might be supposed to give quinaldine and tetrahydro-quinaldine by dismutation.

XIII.
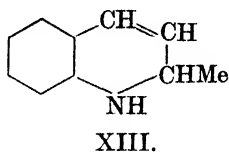
In the products of the Doebner-Miller synthesis, however, no tetrahydroquinaldine can be detected. Secondary bases are, however, formed and consist mainly of ethylaniline and n-butylaniline. These must be formed by reduction of the anils of acetaldehyde, $\phi N:CH \cdot CH_3$, and of crotonaldehyde, $\phi N:CH \cdot CH:CH \cdot CH_3$, and it thus appears that under the conditions of the synthesis the dihydro-quinaldine formed reduces these anils to alkylanilines and is itself oxidized to quinaldine.

The synthesis can be extended by using a mixture of two aldehydes, or of an aldehyde and a ketone. An example is the preparation of α-alkyl-β-naphthacinchoninic acids by heating an alcoholic solution of β-naphthylamine (1 molecule), pyruvic acid (one molecule) and an aldehyde (about two molecules), when the high-melting cinchoninic acid derivative separates on cooling.
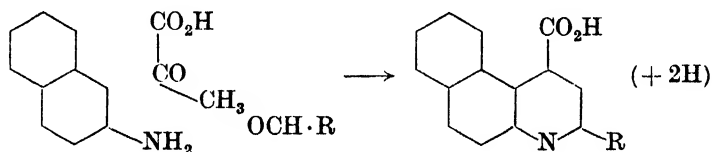
This reaction can be used for the identification of aliphatic aldehydes, such as citronellal,[1] the aldehyde being recognized by the melting-point of the naphthacinchoninic acid derived from it.

(vi) Quinolines may be obtained by the intramolecular condensation of compounds of the type of o-amino-cinnamic aldehyde or o-amino-styryl methyl ketone.
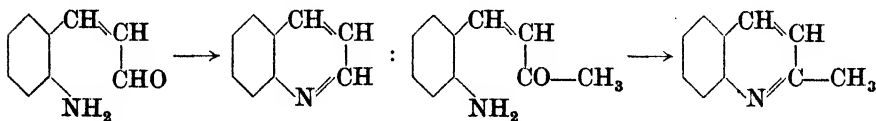
Friedländer's synthesis[2] is a very similar reaction, and is, as opposed to the Skraup reaction, of particular value for the preparation of quinolines substituted in the pyridine nucleus. It consists in the condensation, in presence of alkali, of o-amino-benzaldehyde or an o-aminophenyl ketone

[1] O. Doebner, *Ber.* 1898, **31**, 1888.
[2] P. Friedländer and C. F. Gohring, ibid. 1883, **16**, 1833.

with any compound containing the grouping $\cdot CH_2 \cdot CO \cdot$, such as certain aldehydes (including acetaldehyde), and ketones and ketonic esters. It can be represented by the following equation:
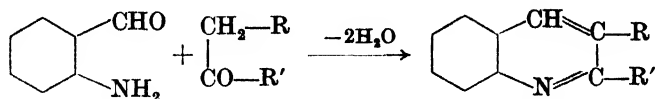
Thus with acetoacetic ester 2-methyl-quinoline-3-carboxylic ester is obtained. The reaction takes place with o-amino-benzaldehyde and has been used for the synthesis of a variety of quinolines substituted in the 2 and 3 positions. The usual condensing agent is caustic soda, though sometimes a trace of piperidine is better.

o-Amino-benzaldehyde is, however, not readily prepared in quantity and hence it is frequently convenient to use isatin in its place.[1] In presence of alkali the isatin ring opens giving the salt of isatinic acid (o-amino-benzoylformic acid), which then reacts normally in the Friedländer synthesis giving a derivative of cinchoninic acid (quinoline 4-carboxylic acid), which loses carbon dioxide on heating to give the simple quinoline.
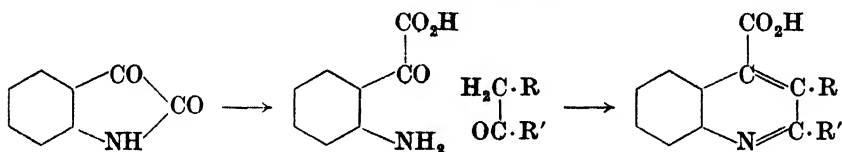
By replacing o-amino-benzaldehyde with anthranilic acid poor yields of 4-hydroxyquinolines have been obtained in some cases.[2]
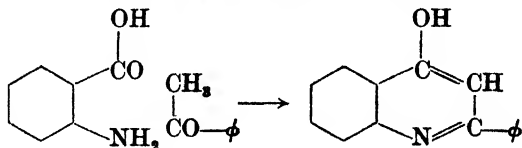
(vii) The condensation of primary aromatic amines with β-ketonic esters is a reaction frequently used for the preparation of 2- and 4-hydroxy-quinolines (2- and 4-quinolones). The nature of the product depends upon the condition of the experiment. At room temperature, aniline and acetoacetic ester combine to form β-anilinocrotonic ester; the latter, when heated for a few minutes at 250°, gives 4-hydroxy-2-methylquinoline.
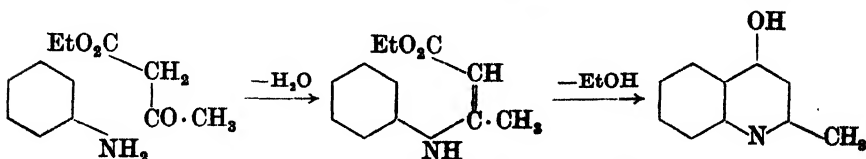
When, however, aniline and acetoacetic ester react together at 110°, aceto-

[1] W. Pfitzinger, *J. pr. Chem.* 1902, **66**, 263.
[2] For applications see H. P. W. Huggill and S. G. P. Plant, *J.C.S.* 1939, **785**.

acetanilide is formed, and this, when warmed with sulphuric acid, yields 2-hydroxy-4-methylquinoline (γ-methylcarbostyril).
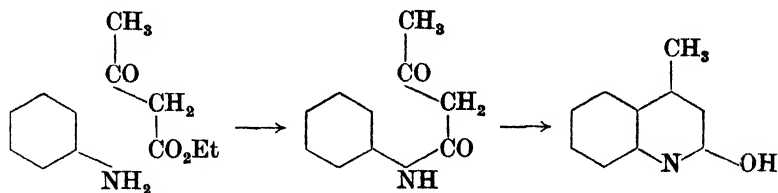
(viii) The conversion of an indole into a quinoline derivative by means of chloroform and alkali has already been mentioned (p. 500). A similar ring enlargement is involved in the conversion of α-methyl-indole into quinoline by passing its vapour through a red-hot tube, which recalls the similar production of pyridine from α-methylpyrrole (p. 521). Another interesting conversion of an indole into a quinoline derivative is the transformation of tryptophane into kynurenic acid (4-hydroxy-quinoline-2-carboxylic acid) when administered to a dog.
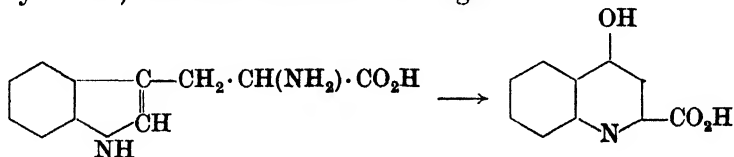
General Properties of Quinoline and Derivatives

Quinoline is a colourless, strongly refracting oil, boiling-point 239°. It is almost insoluble in water, but is somewhat hygroscopic. In its general chemical behaviour it very closely resembles pyridine, and it is unnecessary, therefore, to give a detailed account of all its properties, or of those of its derivatives. Of the salts of quinoline the bichromate is very sparingly soluble in cold water and can be used for its purification. Quinoline resembles pyridine in reacting with sodium, and is best dried with potassium hydroxide or barium oxide.

Quaternary Derivatives. Quinoline combines readily with alkyl halides or sulphates to give salts of the N-alkyl quaternary bases. The hydroxides of these quaternary bases are less stable than in the pyridine series, and solutions obtained by treating the quaternary salts with silver oxide or caustic alkalis deposit white needles of the bimolecular ether (XIV)
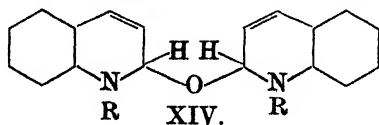
derived from the pseudo-base (see p. 524).[1] As has been mentioned above (p. 525) the pseudo-bases combine very readily with alcohols to give

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[1] A. Hantzsch and M. Kalb, *Ber.* 1899, **32**, 3119; A. Kaufmann and P. Strubin, ibid. 1911, **44**, 683.

alkyl ethers, and this formation of the bimolecular other is simply an example of this general reaction, one molecule of the pseudo-base behaving as an alcohol. The velocity of formation of the ether shows that it is formed in a bimolecular reaction between the molecules of the pseudo-base.[1] The equilibrium between true base and pseudo-base obviously lies much more on the side of the latter than in the case of the pyridinium hydroxides, a fact which probably arises from the less complete conjugation of the heterocyclic ring in the quinoline derivatives. On the other hand, the quaternary hydroxides of quinolines which contain an amino or hydroxyl substituent in the carbon (Bz) ring show no tendency to change into pseudo-bases.[2] The quaternary quinolinium salts react with Grignard reagents in a fashion which recalls the pseudo-basicity of their hydroxides. If phenyl magnesium bromide is added to quinoline methiodide in ether, a violent reaction occurs, and addition of water gives a dihydroquinoline with a phenyl group in the α-position.
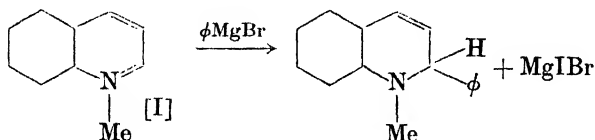
As with the pyridine derivatives, oxidation of the pseudo-bases (i.e. addition of ferricyanide to an alkaline solution of the quaternary salt) gives the N-alkyl-α-quinolone (XV); these compounds resemble the pyridones and their structure offers the same difficulties. If the quinolone is further oxidized with permanganate, the ring is opened and N-alkyl formyl-anthranilic acids (XVI) are formed.

XV.   XVI.
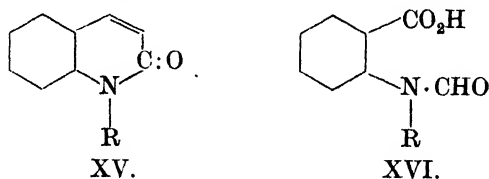
Quinoline forms quaternary derivatives with acid chlorides, and the hydroxides of these change into pseudo-bases which are unstable, and the product, obtained under ordinary Schotten-Baumann conditions, is an acetyl derivative of o-aminocinnamic aldehyde.
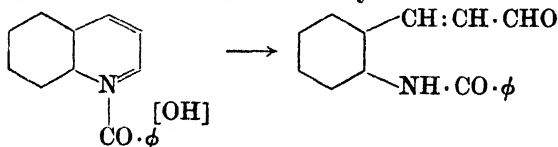
As might be expected from a comparison of the nuclear reactivity of benzene and pyridine, substitution (for example, halogenation, nitration,

[1] J. G. Aston and P. A. Lasselle, *J. Amer. C. S.* 1934, **56**, 426.
[2] H. Decker and H. Engler, *Ber.* 1903, **36**, 1169.

sulphonation) in quinoline takes place in the benzene and not the pyridine ring. Thus nitration with a fuming nitric acid-sulphuric acid mixture gives both 5- and 8-nitroquinoline; further nitration gives 5,7- and 6,8-dinitroquinolines. The 2- and 4-halogenated quinolines (where the halogen atom is in the pyridine nucleus) may be obtained by the action of phosphorus halides on the corresponding hydroxy-quinolines, and the 2-chloro compound is the product of the action of phosphorus pentachloride on the N-alkyl-α-quinolones, as in the pyridine series (see p. 528). The 3-halogen-quinolines can be obtained by the action of the sulphur halides upon quinoline. As in the case of the halogen derivatives of pyridine, the halogen atom in the 2- and 4-halogen-quinolines is reactive, and is easily replaced.

Amino-quinolines containing the amino group in the benzene ring are prepared by reducing the corresponding nitro compounds. The 2- and 4-amino-quinolines are most readily produced from the corresponding halogen-quinolines by the action of ammonia; 3-amino-quinoline is obtained by the Hofmann degradation of the amide of quinoline 3-carboxylic acid. The direct introduction of the amino-group into quinoline by means of sodamide, gives 2-amino-quinoline; this is an attack by an anionoid reagent and substitution must, therefore, take place in position 2 (see p. 529). With the exception of the 2- and 4-amino compounds, which show the same anomalous behaviour as the corresponding amino-pyridines, the amino-quinolines are true aromatic amines and can be diazotized.

Hydroxy-quinolines. Most of the hydroxy-quinolines are obtained from the nitro compounds by reduction and diazotization. They are both tertiary bases and phenols. 8-Hydroxy-quinoline ('oxine') is of considerable interest as an organic reagent for the detection and separation of certain metals, with which it forms insoluble derivatives; it is used chiefly for aluminium, magnesium, and zinc.[1] In these complexes the metal replaces the hydrogen atom of the phenolic group and is also attached by a co-ordinate link from the nitrogen atom, so that the composition of the complex is $(C_9H_6ON)_2M$, if the co-ordination number of the metal is four, or $(C_9H_6ON)_3M$, if it is six. The structure of the former type is:
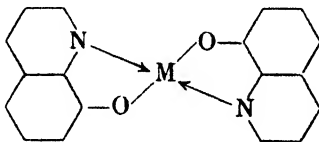
The 2- and 4-hydroxy-quinolines differ from their isomers; they are often called α- and γ-quinolone and their structure raises the same points that have been discussed in the case of the pyridones (see p. 531). 2-Hydroxy-quinoline, usually called carbostyril, is the lactam of *o*-amino-

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[1] See A. D. Mitchell and A. M. Ward, *Modern Methods in Quantitative Chemical Analysis,* Longmans, Green & Co. 1932: *Organic Reagents for Metals,* Hopkin & Williams, Ltd. 1933.

cinnamic acid, and attempts to obtain that acid, as, for example, by reduction of o-nitrocinnamic acid, result in the formation of carbostyril. It is also formed by the action of alkali on o-acetylamino-benzaldehyde.
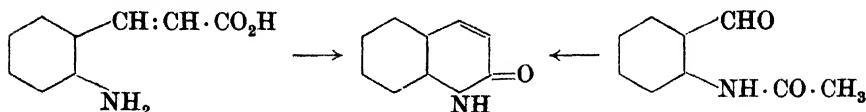
Carbostyril (melting-point 200°) is a very stable solid which sublimes without decomposition; it is very sparingly soluble in cold water, but easily soluble in alcohol and ether. It is extremely weak both as an acid and a base. It is converted into an O-methyl ether (XVII) by diazomethane, and into an N-methyl ether by the action of methyl iodide; the latter is identical with the compound obtained by oxidation of the pseudobase derived from methylquinolinium hydroxide. The structure of the N-methyl ether is usually taken to be (XVIII), although the possibility

XVII.   XVIII.   XIX.   XX.
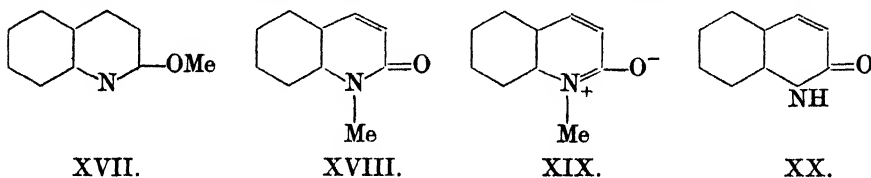
that there is resonance with the zwitterion structure (XIX) is not excluded. Similarly formula (XX) is usually allotted to carbostyril itself.

4-Hydroxy-quinoline is called kynurin. It is obtained from kynurenic acid, 4-hydroxy-quinoline-2-carboxylic acid, which occurs in the urine of dogs fed on meat, by loss of carbon dioxide on heating, and also by ring closure of o-formylamino-acetophenone with alkali.

XXI.
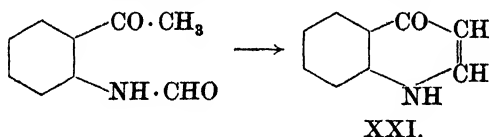
It is a solid (melting-point 201°), sparingly soluble in all organic solvents and crystallizes from water as a trihydrate. It gives rise to both O- and N-ethers and is converted into quinoline when distilled with zinc dust. Its structure is usually taken to be that of γ-quinolone (XXI), but the evidence is very scanty.

Quinoline carboxylic acids are amphoteric in character. In addition to the more obvious modifications of the various quinoline syntheses by which they may be prepared, the quinoline carboxylic acids are produced by the oxidation of the homologues of quinoline with chromic acid. The α-alkylquinolines, which are difficult to oxidize directly, may be first condensed with formaldehyde (see below), the resulting substance being then readily oxidized. Acids with the carboxyl group in the 2- or 4-position can be prepared by taking advantage of the behaviour of quinolinium

cyanides. Just as the quaternary quinolinium hydroxides tend to change into pseudo-bases, so in a quinolinium cyanide the cyanide ion, the anion of a weak acid, tends to become attached by a covalent link either in the 2 or 4 position. If the quaternary compound formed by quinoline and benzoyl chloride is treated with an aqueous solution of potassium cyanide, a white solid is obtained which is 1-benzoyl-2-cyano-1,2-dihydroquinoline. This compound loses benzaldehyde on standing with strong hydrochloric acid and the cyano group is simultaneously hydrolysed, so that the product is quinoline-2-carboxylic acid, which is called quinaldinic acid because it is formed in the oxidation of quinaldine.[1]
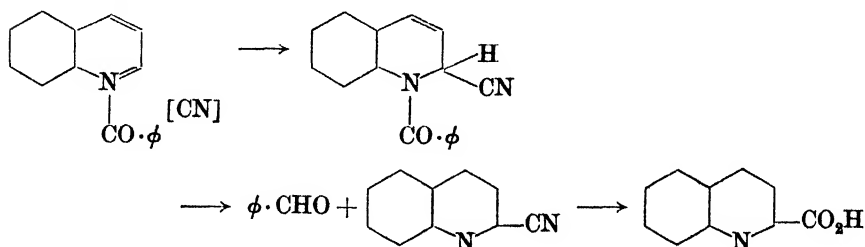
If the N-benzoylquinolinium salt is replaced by quinoline methiodide or methosulphate, there is the same migration of the cyano group to the ring, but, for reasons which are unknown, it enters the 4 and not the 2 position. The resulting 1-methyl-4-cyano-1,4-dihydroquinoline is then oxidized in pyridine solution with iodine, when 4-cyano-1-methylquinolinium iodide is formed, and this on dry distillation loses methyl iodide to give the nitrile of quinoline-4-carboxylic acid.[2]
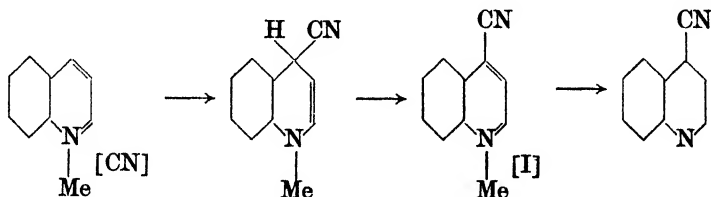
Hydrolysis of the nitrile gives the acid which is called cinchonic (or cinchoninic) acid, because it is the main product of the oxidation of the alkaloid cinchonine. Quinic acid, formed in the oxidation of quinine, is 6-methoxycinchonic acid, and can be synthesized from 6-methoxyquinoline in a similar way.

Homologues of Quinoline. The homologues of quinoline which are of the greatest interest are quinaldine (2-methylquinoline) and lepidine (4-methylquinoline). Both of these occur in coal-tar, and the latter is also produced by distilling cinchonine with potassium hydroxide. In these two compounds the methyl groups are reactive in that they condense with benzaldehyde to give benzylidene-quinaldine and benzylidene-lepidine,

[1] A. Reissert, *Ber.* 1905, **38**, 1603.   [2] A. Kaufmann, ibid. 1918, **51**, 116.

$C_9H_6N \cdot CH:CH\phi$, and also the corresponding diquinaldine and dilepidine compounds, $(C_9H_6N \cdot CH_2)_2:CH\phi$.
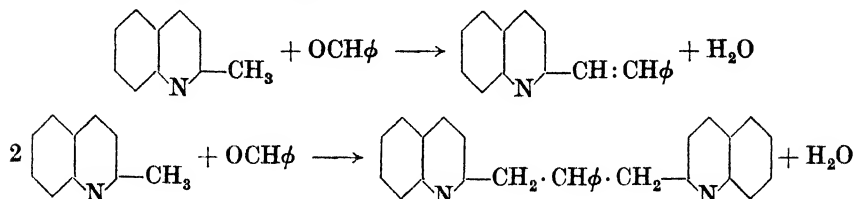
This reactivity is also shown by 2- and 4-alkylquinolines containing the group $\cdot CH_2R$, but never by the 3-alkyl compounds. Precisely the same reactivity is observed in the α- and γ-methylpyridines (see p. 534) and in 1-methylisoquinoline. The pyridine nucleus is not essential: the same reactivity is found in certain methyl derivatives of other heterocyclic nitrogen compounds, such as 2-methyl and 2,3-dimethylquinoxaline, which react with benzaldehyde to give the following mono- and di-benzylidene derivatives, respectively.[1]

Benzaldehyde can be replaced by other aldehydes, and the condensation is brought about by heating with zinc chloride, hydrochloric acid, or acetic anhydride, or sometimes merely by heating the reactants together. With certain aldehydes, such as chloral, quinaldine gives a hydroxy compound and not an ethylene:
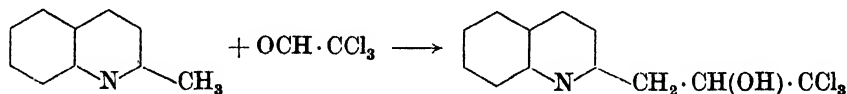
and the analogous compound from quinaldine and benzaldehyde can be obtained by exposing them to sunlight for some months.[2] The reactivity of the methyl group in quinaldine is shown in other reactions: for example, it can be condensed with oxalic ester in presence of potassium ethoxide to give α-quinolyl-pyruvic ester.[3]
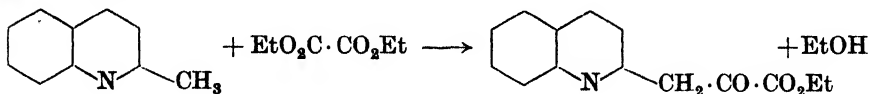
In these condensations the methyl groups of α- and γ-methyl-pyridines and -quinolines bear a strong resemblance to those in methyl ketones $(R \cdot CO \cdot CH_3)$ and in compounds such as 2,4-dinitrotoluene; in all these cases the reactivity of the methyl group arises from some kind of inter-

[1] G. M. Bennett and G. H. Willis, *J.C.S.* 1928, 1960.
[2] A. Benrath, *J. pr. Chem.* 1906, **73**, 386.
[3] W. Wislicenus and E. Kleisinger, *Ber.* 1909, **42**, 1140.

action between the methyl group and the activating group, which is the carbonyl group in the methyl ketones and the nitro groups in dinitrotoluene. With the methyl ketones the nature of the interaction is known in certain reactions to be enolization, the structure $\cdot CO \cdot CH_2 \cdot$ undergoing ready isomeric change into $\cdot C(OH):CH$. In quinaldine and analogous compounds the activating group must be the nitrogen atom of the ring, and the question presents itself as to the nature of the interaction between this atom and the methyl group which causes such marked reactivity in the latter.

Two important sets of observations have been made which throw considerable light on this question. The first is that the reactivity of the methyl group is determined in a particular way by its position with respect to the nitrogen atom. The fact has already been pointed out that in β-methyl quinolines the methyl groups do not show any of the characteristic condensation reactions which appear in the α- and γ-methyl compounds, but a more important observation is that of Mills,[1] who showed that of the two methyl-isoquinolines in which the methyl group is attached to a carbon atom next to the cyclic nitrogen atom, only the 1-methyl compound (I) contains a reactive methyl group.

I.   II.
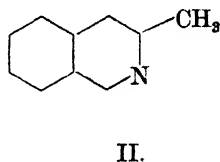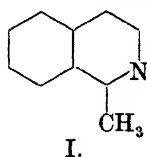
When these two compounds are heated with benzaldehyde and a little zinc chloride, the first readily gives 1-styryl-isoquinoline,

$$C_9H_6N \cdot CH:CH \cdot \phi,$$

while with the 3-methyl compound (II) there is no reaction and the methyl-isoquinoline and benzaldehyde can be recovered unchanged. This shows that attachment of a methyl group to the carbon atom next to the nitrogen atom is not sufficient to make it reactive and some other conditions must be fulfilled. This view is supported by analogous observations with 4-phenyl-2-methylthiazole (III) and 2-phenyl-4-methylthiazole (IV).

III.   IV.
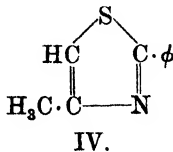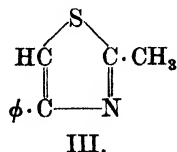
Only the 2-methyl compound (III) gives condensation reactions with aldehydes.

The second set of observations deal with the quaternary derivatives of α- and γ-methyl-quinolines and analogous compounds. If quinaldine is

[1] W. H. Mills and J. L. B. Smith, *J.C.S.* 1922, **121**, 2724.

converted into its methiodide, the reactivity of the α-methyl group becomes much more pronounced than with quinaldine itself, and this effect is general with all heterocyclic compounds containing reactive methyl groups. The same conditions, however, hold as to the position of the methyl group with respect to the nitrogen atom. Conversion of a β-methyl quinoline into the methiodide does not confer any reactivity on the methyl group, and the methiodide of 3-methyl isoquinoline is as incapable of condensing with benzaldehyde as the tertiary base itself. With the α- and γ-methyl-quinolines not only is there an increase in reactivity, but the conditions under which condensation reactions take place are changed. Quinaldine methiodide condenses with benzaldehyde in alcoholic solution at room temperature in the presence of a small quantity of an alkaline condensing agent, such as piperidine, to give a styryl compound, while a similar reaction between quinaldine and benzaldehyde only takes place on heating with an acidic reagent such as zinc chloride or hydrochloric acid. Further, condensation will take place with an aromatic nitroso compound, such as nitrosobenzene or p-nitroso-dimethylaniline, to form an anil, and a corresponding reaction is not known with quinaldine itself.
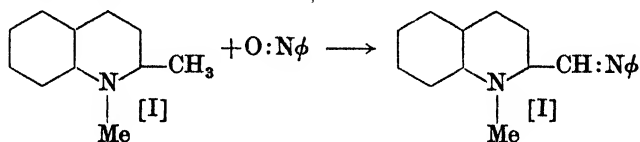
Now the importance of the quaternary derivatives for our present purpose is that with them it is much easier to explore the mechanism of these condensations and the function of the condensing agent, and the conclusions which can be reached throw light on the possible mechanisms of reaction in the tertiary compounds. As has been mentioned above (p. 549), treatment of a quaternary quinoline salt with alkali gives the quaternary hydroxide, but the latter compound is often unstable and tends to change into a non-electrolyte. When there is a methyl or methylene group in the α or γ position in the ring, this non-electrolyte is an anhydro base, formed by loss of water from the quaternary hydroxide.
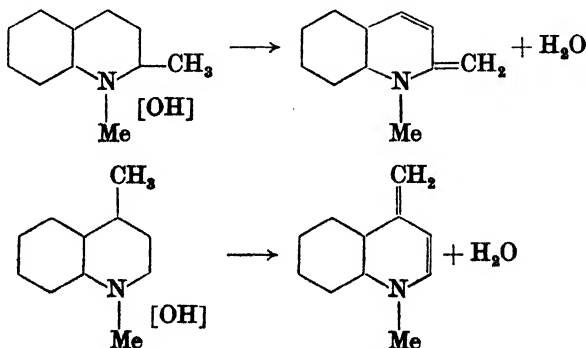
The anhydro bases of this type, often called methylene bases, are unstable and reactive compounds easily oxidized in air, and it is difficult to isolate them as pure substances. In a few cases, however, they have been purified and analysed. One example is the methylene base from quinaldine methosulphate and caustic soda,[1] and a more important case is that derived from β-naphthapyridine ethiodide (V).
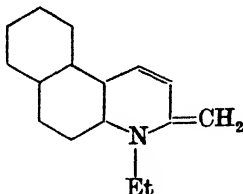
V.

Because of its higher molecular weight this compound is less soluble and more stable than the corresponding quinaldine derivative, and by using it Mills was able to demonstrate the actual mechanism of the condensation of naphthaquinaldine ethiodide with aldehydes.[2] He found that this methylene base condenses with p-dimethylamino-benzaldehyde without the need for any condensing agent to give a compound which contains no oxygen and must have the structure (VI). This condensation product gives with hydriodic acid p-dimethylamino-benzylidene-β-naphthaquinaldine ethiodide, the same product which is obtained by the interaction of the aldehyde and the quinaldine ethiodide in presence of piperidine.
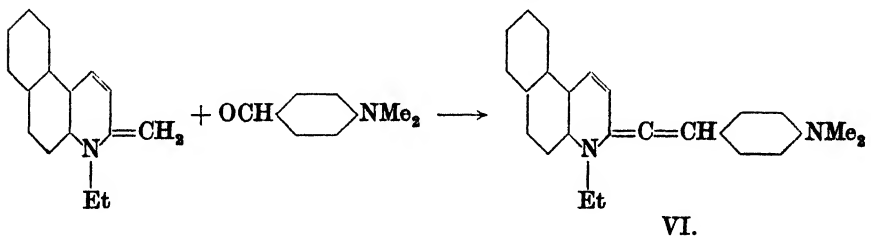
VI.
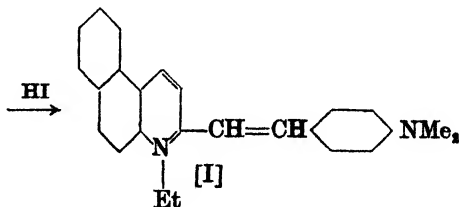
VII.

Further, the first condensation product (VI), which contains the reactive allene grouping $(:C:C:C:)$, was shown to abstract hydriodic acid from piperidine hydriodide and form the final product (VII).

[1] E. Rosenhauer, *Ber.* 1926, **59**, 946.
[2] W. H. Mills and R. Raper, *J.C.S.* 1925, **127**, 2466.

These important observations make it almost certain that the mechanism of the condensation of the quaternary salt in presence of piperidine consists of, first, the removal of hydriodic acid from the quaternary iodide to give the methylene base; next, the condensation of the methylene base and the aldehyde to give the allene compound; and finally the interaction of this compound with the piperidine hydriodide formed in the first stage to give the final product and piperidine; the latter is then able to enter on another cycle of changes, and thus only a small amount of the condensing agent is needed. Since the methylene base is an essential intermediate in the reaction, only those quinolinium compounds which give methylene bases will enter into these condensation reactions. The absence of reactivity in the methyl group of a quaternary β-methylquinoline must thus be due to the fact that a methylene base cannot be formed, and this fact is not surprising. The only structure that can be written for a β-methylene base would be:
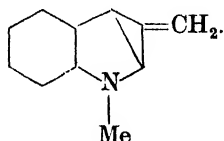
There is no other way in which the valencies of the constituent atoms can be accounted for. This structure, however, is similar to that of a meta-quinone in the benzene series and is, of course, extremely improbable (see p. 268). The link between the α- and γ-carbon atoms would necessarily be much longer than that for a normal carbon-carbon covalency, and there is considerable evidence that this distance cannot vary to such an extent.

These observations and the deductions made from them have a direct bearing on the reactivity of the methyl group in the α- and γ-methyl tertiary bases such as quinaldine itself. They suggest that the absence of reactivity in the β-methyl compounds is due to the impossibility of formation of some reactive intermediate compound of structure analogous to that of the methylene bases, and that such an intermediate is formed from the α- and γ-methyl compounds. There is, however, no direct experimental evidence of the existence of this reactive intermediate compound, and consequently the question as to the mechanism of the condensation reactions and the cause of the reactivity in the tertiary bases is much more difficult to answer with precision than is the case with the quaternary compounds.

If the attempt is made to formulate a more definite answer to this question, there are several possibilities which merit discussion. One possibility is to say that the reactive form of the α- and γ-methyl quinolines has a structure analogous to that of the methylene bases of the quaternary series and is formed from the tertiary base by a tautomeric change, in which a hydrogen atom leaves the methyl group and becomes attached to the nitrogen atom.
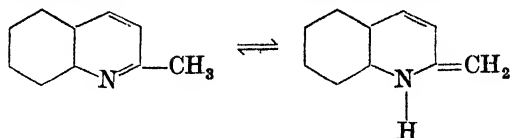
Since the commonest type of tautomeric change takes place in a system of three atoms linked by one single and one double bond, e.g.

$$O{=}C{-}CH_2{-} \;\rightleftharpoons\; HO{-}C{=}CH{-},$$
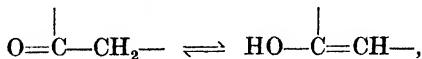
this view can be held to lead to the conclusion that in quinaldine there is a true double bond between the nitrogen and α-carbon atoms, and that it is the presence of this double bond, shown in the above formula, which makes the tautomeric change possible. If a similar arrangement of fixed double bonds is assumed in isoquinoline, the absence of reactivity in the 3-methyl compound would be explained by the absence of a double bond between the nitrogen atom and the carbon atom which carries the methyl group.
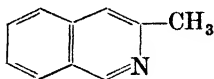
On the other hand, in 1-methylisoquinoline there is a double bond in the right place and tautomeric change is possible.
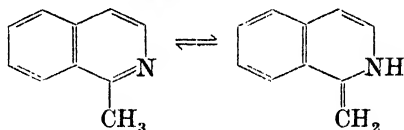
This view can clearly be extended to the two thiazoles which have been quoted above. If this suggestion is adopted, the function of the condensing agent is presumably to increase the rate of tautomeric change, a function which could be paralleled with that of condensing agents in certain reactions which involve a keto-enol tautomer. The reactivity of the methyl groups in the quaternary compounds which has been discussed already could obviously be explained on the same basis. A methyl group in the β position is unreactive and in what has been said above this has been attributed to the impossibility of the existence of a β-methylene base; it is possible to go further and say that the formation of a β-methylene base is precluded by the fixed arrangement of the double and single bonds in the ring system.

The chief objection that can be raised against a view of this kind is not so much against the need that it implies for the formation of an intermediate compound containing the methylene group, as against the further conclusion that the double bonds in quinoline and isoquinoline are in fixed positions and that it is the position of the methyl group with respect to these fixed double bonds which determines the reactivity. If the double bonds do indeed occupy fixed positions, it seems a necessary consequence

that the distances between the doubly linked carbon atoms and that between the singly linked carbon atoms should be different. There is no accurate knowledge of the distances between the atoms in quinoline and isoquinoline, but it seems very unlikely that there can be any essential structural difference between these compounds and naphthalene, and in this latter compound determination of the structure by the X-ray method shows that the molecule consists of two regular hexagons, and the distances between any two linked carbon atoms is the same.[1] If for this reason the actual fixation of the double bonds is rejected, something of the original suggestion remains, but it must be formulated differently. The necessity for the existence of a reactive intermediate compound of methylene structure can still be assumed, but the absence of reactivity in β-methyl quinoline and 3-methyl isoquinoline must be explained by saying that the methylene compounds derived from them would have impossible structures, analogous to no known compound, and hence do not exist. Their structures would be:
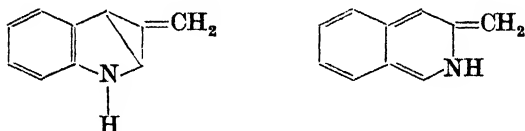
The first of these is similar to the unknown metaquinones; in the second the conjugated system of the benzene ring has disappeared, and the structure is similar to the unknown 2,3-naphthaquinones. The difference in reactivity between 1-methyl and 3-methylisoquinoline would then be attributed to the impossibility of the formation of a methylene compound from the latter, and not to any essential difference in the nature of the bonds uniting the atoms which form the heterocyclic ring.

Whether there is any actual tendency for quinaldine to undergo isomeric change into a methylene compound is, of course, not directly proved by experiment, but rather deduced from the behaviour of the quaternary compounds. The marked difference in the nature of the agent necessary to bring about condensation of an aldehyde with a tertiary base and a quaternary salt suggests another possibility. In the majority of cases the tertiary compounds need an acidic reagent, such as hydrochloric acid or zinc chloride. It may well be that the function of this acidic compound is to combine with the tertiary base and convert it into a quaternary compound which then at a higher temperature can give up the acid again, possibly to another molecule of tertiary base, and so be converted into a methylene base. On this view the mechanism of reaction with the tertiary compounds would be almost indentical with that of the quaternary salts:
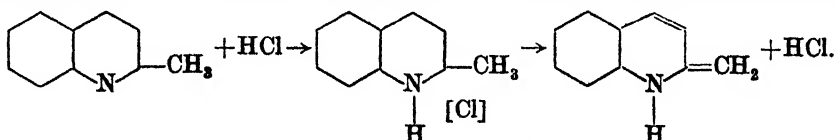
[1] J. M. Robertson, *Proc. Roy. Soc.* 1933, 142, A, 674.

A substance such as zinc chloride could behave in a similar manner, the nitrogen atom becoming attached to zinc by a co-ordinate link, as it is known to be in the zinc ammine compounds.
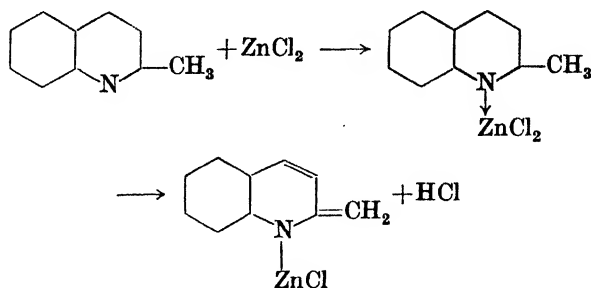
Although a mechanism of this kind provides a comparatively satisfactory explanation of many of the known facts, it clearly cannot embrace them all. The condensation of quinaldine with oxalic ester which is brought about by potassium ethoxide is a reaction in which the nitrogen atom must be tertiary throughout, and there can be no quaternary compound which might be converted into a methylene base. There is no experimental evidence whatever as to the mechanism of this reaction, and hence it is premature to discuss the various possibilities it presents. Similarly in the photochemical condensation of quinaldine with aldehydes there is no knowledge of the nature of the activation of the reacting molecules by the absorbed radiation.

In conclusion it should be pointed out that although the formation of a reactive methylene compound seems to be involved in certain of the condensation reactions of quinaldine and similar compounds, and has direct experimental support in the case of the quaternary compounds, there are differences in the reactivity of other groups attached to the α and γ positions on the one hand and the β position on the other, for which no analogous explanation can possibly be offered. Mills[1] has drawn attention to the fact that if a reactive methyl group is replaced by a chlorine atom, the chlorine atom in the resulting compound shows an exceptional reactivity. The difference between α-chloroquinoline and the β-isomer has been described above. This generalization holds not only for the heterocyclic bases, but for other classes of compounds; thus the reactive methyl group of a methyl ketone, $\cdot CO \cdot CH_3$, gives the reactive acid chloride $\cdot CO \cdot Cl$, and 2,4-dinitrotoluene corresponds to the reactive 2,4-dinitrochlorobenzene. The reactivity of the methyl groups in all these compounds finds a ready explanation in isomeric or tautomeric change into a more reactive isomer, but there is no such possibility in the chloro compounds.

Cyanine Dyes. The reactivity of the methyl groups in the α- and γ-methylquinolines and similar substances is made use of in the preparation of the important cyanine dyes, of which only a brief mention can be made

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[1] *J.C.S.* 1922, **121**, 2731.

here.[1] These dyes are salts in which the kation consists of two heterocyclic nuclei, each containing a nitrogen atom; an odd number of carbon atoms separates the two nitrogen atoms, and these carbon atoms form a conjugated system of single and double bonds.[2] The kation carries one positive charge and hence one nitrogen atom is quaternary and the other tertiary. An example is 1,1'-diethyl-pseudocyanine iodide, the formula of which can be written as in (XIII *a*). In such a system, however, it is impossible to say that one nitrogen atom is permanently quaternary and the other tertiary, since by a shift in distribution of the electrons the first becomes tertiary and the second quaternary without the need for the movement of any atom. Hence the formula of the dye can also be written as in (XIII *b*), and the actual constitution of the kation is that of a resonance-hybrid of these two structures.

XIII *a*.   XIII *b*.
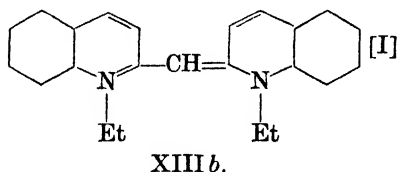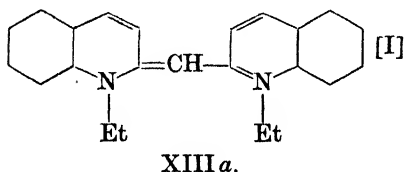
Each hetero-ring is benzenoid in one of these formulae and quinonoid in the other. Resonance between two such structures is known to give intense absorption in the visible part of the spectrum in other compounds; examples already mentioned in this book are the triphenylmethane dyes (p. 93) and the nitrogen free radicals, such as ϕ_2N (p. 390). The intense colour of the cyanines thus seems to have the same cause as that of many other classes of dyes.

The cyanine dyes are of no use as dye-stuffs since they fade almost immediately on exposure to light, but are used as sensitizers for photographic plates or films. The untreated photographic plate is sensitive mainly to blue and ultra-violet light, but if it is treated with certain dye-stuffs, it becomes sensitive to those wave-lengths where the dye has an absorption band, and the sensitivity of the plate can be extended towards the red. In the cyanine dyes the longer the conjugated chain which unites the two heterocyclic nuclei, the further the absorption bands and the sensitization extend towards the red; with dyes containing a seven-membered chain, ·CH:CH·CH:CH·CH:CH·CH·, the tricarbocyanines, the plate becomes sensitive to the near infra-red outside the visible region.[3] The precise function of the sensitizers is but little understood, but it is clear that they absorb light, say in the infra-red, and convert it into some form of energy which acts upon the silver halide in such a way as to make the halide readily reducible to the metallic state.

[1] Useful summaries of the chemistry of the cyanine dyes are M. Q. Doja, *Chem. Rev.* 1932, **11**, 273, and F. M. Hamer, *Dictionary of Applied Chemistry*, J. F. Thorpe, Supplement, 1934, **1**, 358.   [2] W. H. Mills and H. G. Ordish, *J.C.S.* 1928, 82.
        [3] N. I. Fisher and F. M. Hamer, ibid. 1933, 189; *Proc. Roy. Soc.* 1936, **154**, A, 703.

The apocyanines[1] passess the two heterocyclic nuclei in direct union (α position united to a β position); where one $\cdot$CH: group separates the two nuclei, we have the pseudo-cyanines (2,2'-attachment as in formula (XIII) above), the iso-cyanines (2,4'-attachment), and the cyanines (4,4'-attachment). Where the nuclei are separated by the group $\cdot$CH:CH$\cdot$CH$\cdot$ in the 2 and 2' positions we have the important carbocyanine class. The preparation of these dyes involves the reactivity of an α- or γ-methyl group in quinolines and other similar cyclic systems. For example, the 1,1'-diethyl-pseudo-cyanine iodide (XIII) above, is prepared by the action of alcoholic potassium hydroxide upon a mixture of 2-iodo-quinoline ethiodide and quinaldine ethiodide.
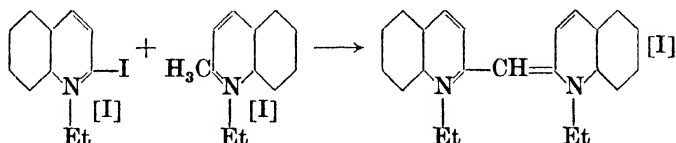
An example of the preparation of a carbocyanine is that of pinacyanol from quinaldine ethiodide and ethyl orthoformate (chloroform or form-aldehyde may also be employed to furnish the central carbon atom).
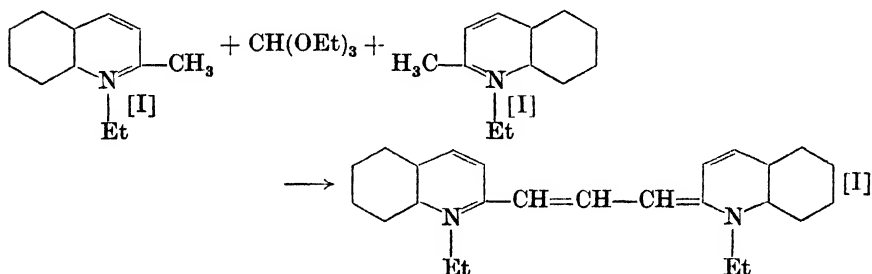
The Reduction Products of Quinoline. The reduction of quinolines leads to varying results according to the experimental conditions. The pyridine ring is much more readily reduced than the benzene ring, and with reagents such as sodium and alcohol, tin and hydrochloric acid, and hydrogen and nickel at 160–180°, it takes up four atoms of hydrogen to give 1,2,3,4-tetrahydro-quinoline (XIV).

XIV.
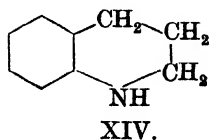
This substance behaves like a monoalkylaniline; it gives an N-nitroso derivative which is easily converted into 6-nitroso-tetrahydro-quinoline, and forms diazoamino compounds which can be transformed into the 6-azo derivatives. Quinolines which are alkylated in the pyridine ring are easily

[1] Their structure is not quite analogous to that of other cyanines; see W. H. Mills and H. G. Ordish, loc. cit.'

reduced, but the product contains a certain amount of the 5,6,7,8-tetra-hydro compound, in which the benzene ring has been reduced. The greater the number of such alkyl groups the greater is the proportion in which this tetrahydro compound is formed; with 2,3,4-trimethylquinoline there is no reduction of the pyridine ring at all.[1] Tetrahydroquinolines are oxidized to quinolines by means of chromic acid, silver acetate, mercuric nitrate, or iodine. The reduced ring in 1,2,3,4-tetrahydroquinoline behaves in many ways like a piperidine ring; the ring is opened by the action of phosphorus pentachloride on the N-benzoyl compound and of cyanogen bromide on the N-alkyl compounds (compare p. 539). On the other hand, exhaustive methylation does not break the ring, since dimethyltetra-hydroquinolinium hydroxide simply loses methyl alcohol on heating. If, however, the quaternary hydroxide is reduced with sodium amalgam, the ring opens to give dimethyl-γ-phenyl-propylamine.[2]
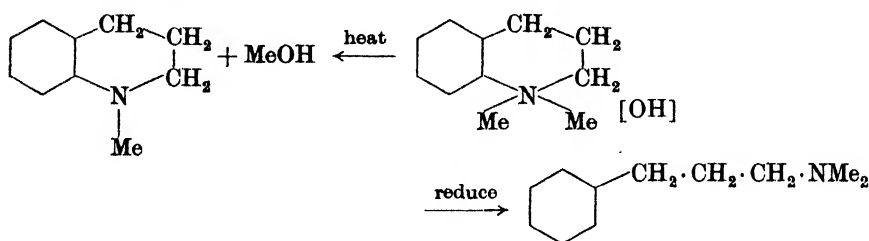
This latter reaction is called Emde's reaction and has found useful applications in alkaloid chemistry.[3]

The complete reduction of quinoline to decahydro-quinoline is brought about by hydriodic acid and phosphorus, or by a variety of vigorous catalytic processes. Decahydro-quinoline exists in two stereoisomeric forms which are analogous to the *cis*- and *trans*-decalins (decahydro-naphthalenes). In one the valencies which join the two rings together lie on the same side of each ring, while in the other they are on opposite sides of each ring; because of the asymmetry introduced by the nitrogen atom both forms are optically resolvable.[4]

A curious reaction occurs when quinoline vapour and hydrogen are passed over nickel at 260–280°. The product contains *o*-toluidine and α-methyl indole, the latter probably arises by dehydrogenation of an intermediate open-chain compound.
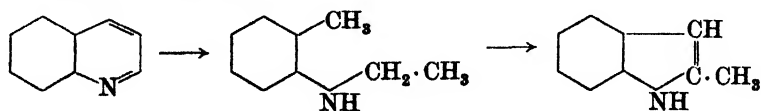
[1] J. v. Braun, W. Gmelin, and A. Petzold, *Ber.* 1924, **57**, 382.
[2] J. v. Braun, ibid. 1916, **49**, 501.
[3] See H. Emde and H. Kull, *Arch. Pharm.* 1934, **272**, 469; P. Groenewoud and R. Robinson, *J.C.S.* 1934, 1692.
[4] W. Hückel and F. Stepf, *Annalen*, 1927, **453**, 163.

ISOQUINOLINE

Isoquinoline (3,4-benzopyridine) is found with quinoline in coal-tar, and crude quinoline from this source contains about 4 per cent. of its isomer. The two can be separated by fractional crystallization of the mixed sulphates, isoquinoline sulphate being the less soluble. Alternatively it may be separated from quinoline by extraction with dilute sulphuric acid, owing to the fact that it is the more basic of the two. This increased basicity is to be ascribed to the fact that the nitrogen atom is not directly united to the benzene nucleus. The nucleus of isoquinoline is found in a number of important alkaloids, for example, papaverine, narcotine, hydrastine, berberine, the anhalonium alkaloids, &c.

The structure assigned to isoquinoline is fully confirmed by a variety of synthetical methods. Isoquinoline derivatives may be synthesized by ring closure of benzene derivatives of the types ϕ—C—N—C—C or ϕ—C—C—N—C, or by building up the pyridine ring from ortho-phenylene derivatives with the structure $C_6H_4{<}^C_C$.

An example of the first type of ring closure is the production of iso-quinoline from benzylidene-amino-acetal by warming with sulphuric acid:
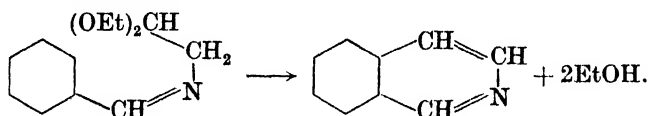
This type of ring closure is of limited application, and it has been shown by P. Staub[1] that in order to obtain isoquinolines from derivatives of structure ϕ—C—N—C—C two conditions are necessary, (1) that the chain should contain a real or potential system of conjugated double links, and (2) that the terminal carbon atom should carry an OH or O-alkyl group. An apparent exception to this rule is the production of isoquinoline by the action of fuming sulphuric acid upon benzylamino-acetaldehyde;[2] in this reaction the benzyl compound may be oxidized to the benzal compound.
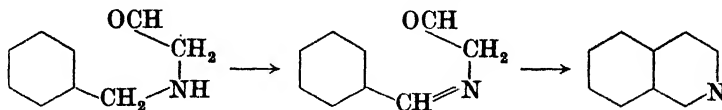
A genuine exception is the formation of isoquinoline by passing the vapour of benzylidene-ethylamine, $\phi \cdot CH:N \cdot CH_2 \cdot CH_3$, through a red-hot tube.
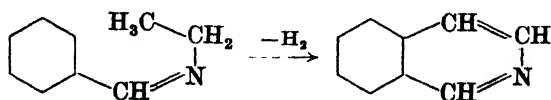
An example of the second type of ring closure is the important method

[1] *Helv. Chim. Acta*, 1922, **5**, 888.   [2] E. Fischer, *Ber.* 1893, **26**, 764.

first introduced by A. Bischler and B. Napieralski[1] and later modified by Pictet[2] and by Decker.[3] It consists in treating the acyl derivatives of β-phenylethylamines with powerful dehydrating agents, such as phosphorus pentoxide, in boiling toluene, xylene, or tetralin, whereby a 3,4-dihydro-isoquinoline is produced.
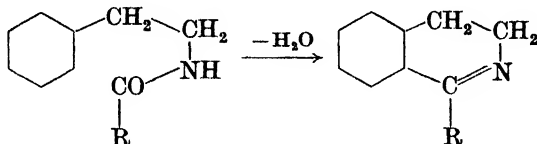
The acyl group may be either aliphatic or aromatic but the yields are poor in the case of the formyl derivative. In general the reaction proceeds most readily when the benzene nucleus is activated by an alkoxyl group in position 3, or by alkoxyl groups in positions 3 and 4. The dihydro-isoquinoline can be oxidized to the true quinoline either by potassium permanganate in acid solution, or by catalytic dehydrogenation with palladium at 150–180°.[4] Many of the isoquinoline alkaloids have been synthesized by this important method. If this reaction is applied to the acyl derivatives of amino-methyl-phenyl-carbinols, isoquinolines are produced directly.
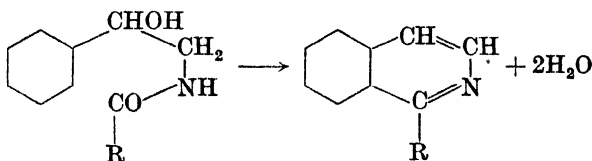
A very similar reaction is the production of tetrahydro-isoquinolines by condensing β-phenylethylamines with aldehydes in presence of hydrochloric acid.[5]
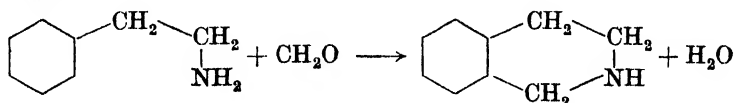
In the case of β-3,4-dihydroxy-phenylethylamine hydrobromide in M/25-aqueous solution with M/12·5-acetaldehyde an 83 per cent. yield of the tetrahydro-isoquinoline is obtained in three days at ordinary temperature.[6]

An example of the production of isoquinoline from an ortho-phenylene derivative, $C_6H_4\langle{}^C_C$, is furnished by the action of phosphorus pentachloride on homophthalimide. The ammonium salt of homo-phthalic acid yields the cyclic imide when heated, and when this is treated with phosphorus

[1] Ber. 1893, 26, 1903.
[2] A. Pictet and F. W. Kay, ibid. 1909, 42, 1973.
[3] H. Decker and W. Kropp, ibid. 2075.
[4] E. Späth, F. Berger, and W. Kuntara, ibid. 1930, 63, 134.
[5] A. Pictet and T. Spengler, ibid. 1911, 44, 2030.
[6] C. Schöpf and H. Bayerle, Annalen, 1934, 513, 190.

pentachloride, 1,3-dichloro-isoquinoline is produced, from which quinoline is obtained by reduction with hydriodic acid and red phosphorus, or zinc dust.
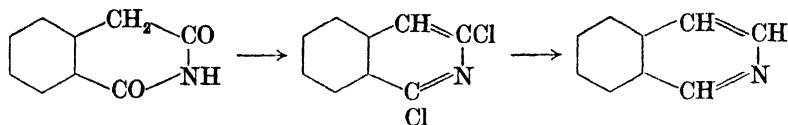
The reaction may also be carried out in one operation by heating homophthalimide with zinc dust in a stream of hydrogen.

An interesting synthesis of an isoquinoline is by the action of sodium ethylate upon phthalylglycine ester, when the carboxylic ester of 4-hydroxy-isocarbostyril is formed.[1]
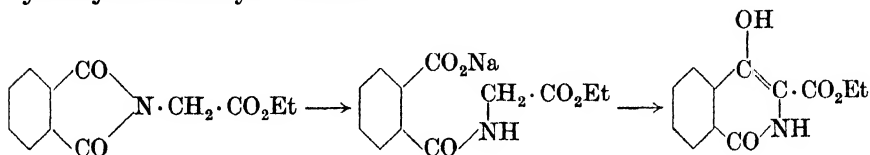
Isoquinoline itself can be synthesized very simply by heating the oxime of cinnamic aldehyde with phosphorus pentoxide. If this reaction were a simple dehydration the product should be quinoline and not isoquinoline, and the production of the latter must be accounted for by supposing that the oxime first undergoes the Beckmann rearrangement, which is followed by ring closure.[2]
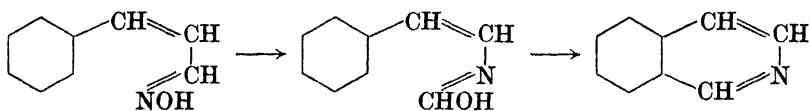
General Properties

Pure isoquinoline is a solid, melting-point 24°, boiling-point 240°, with an odour recalling that of benzaldehyde. It is a strong tertiary base giving well-defined salts, and it combines vigorously with alkyl halides to give the quaternary ammonium salts (I). Like the corresponding salts derived from quinoline, treatment of the quaternary isoquinolinium salts with alkali gives the pseudo-bases, which are 1-hydroxy-1,2-dihydro-isoquinolines (II), and are oxidized by potassium ferricyanide to give the N-alkyl-isoquinolones (N-alkylisocarbostyrils III).

<table>
<tr><td>I.</td><td>II.</td><td>III.</td></tr>
</table>
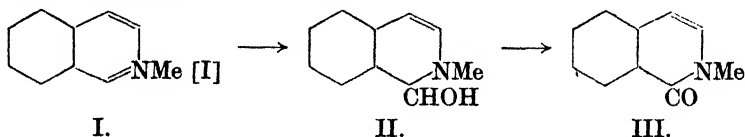
[1] S. Gabriel and J. Colman, *Ber.* 1900, **33**, 980.

[2] Other methods of synthesizing isoquinolines will be found in *The Synthesis of Nitrogen Ring Compounds*, by C. Hollins, London, 1924.

Isocarbostyril itself may be obtained by the action of alcoholic ammonia upon isocoumarin. On methylation it yields both O- and N-ethers; the latter is identical with N-methyl-isoquinolone (III), and the former is 1-methoxy-isoquinoline.. The fine structure of isocarbostyril is uncertain; there are clearly the same possibilities of a ketonic, a hydroxylic, and a zwitterion form as with the α- and γ-pyridones and quinolones (see p. 532). The 1 position in isoquinoline resembles the 2 and 4 positions in pyridine and quinoline; a chlorine atom or methyl group in this position is reactive, and if isoquinoline is heated with sodamide, the 1-amino compound is formed.[1] The 3 and 4 positions do not show these properties and resemble the 3 position in quinoline.

The oxidation of isoquinoline with potassium permanganate in acid solution leads to partial disruption of both rings with the simultaneous production of phthalic and cinchomeronic acids.
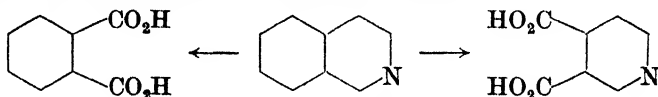
The reduction of isoquinoline, like that of quinoline, takes place first in the pyridine ring, with production of 1,2,3,4-tetrahydroisoquinoline. The reduction is readily carried out with sodium and alcohol, with nickel and hydrogen, or with tin and hydrochloric acid. An interesting synthesis of tetrahydro-isoquinoline is by the action of aluminium chloride upon β-phenylethylglycyl chloride, carbon monoxide being evolved.[2]
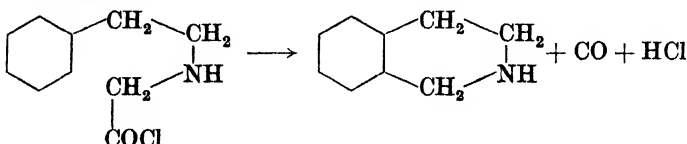
The reaction recalls the production of chloroform by treating dichloro-acetyl chloride with aluminium chloride:[3]

$$CHCl_2 \cdot COCl \longrightarrow CHCl_3 + CO.$$
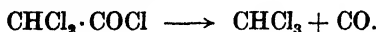
Tetrahydro-isoquinoline shows all the properties of an alkylated benzyl-amine, and is a powerful secondary base which absorbs carbon dioxide from the air. Hofmann's process of exhaustive methylation leads to the production of o-dimethylaminomethyl-styrene, $CH_2{:}CH \cdot C_6H_4 \cdot CH_2 \cdot NMe_2$; it will be recalled that the ring of tetrahydro-quinoline is not opened in this way. When the quaternary hydroxide obtained from the methylation of tetrahydro-isoquinoline is reduced with sodium amalgam (Emde's reaction), dimethyl-β-o-tolylethylamine is formed.
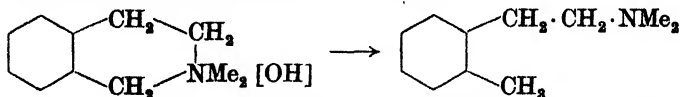
[1] A. E. Tschitschibabin and M. P. Oparina, *Zent.* 1923, iii, 1023.
[2] J. v. Braun and K. Wirz, *Ber.* 1927, 60, 102.
[3] J. Böeseken, *Proc. K. Akad. Wetensch. Amsterdam*, 1909, 12, 417.

The N-benzoyl derivative of tetrahydro-isoquinoline is oxidized by potassium permanganate to the N-benzoyl derivative of o-carboxy-β-phenylethylamine, $HO_2C \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot NH \cdot CO\phi$.

Catalytic reduction of isoquinoline in presence of colloidal platinum leads to cis-decahydro-isoquinoline:[1] the trans compound has been obtained by reduction of trans-hexahydro-homophthalimide.[2]

ACRIDINE AND PHENANTHRIDINE

Acridine and phenanthridine are the two isomeric dibenzopyridines (I) and (II). There are two methods in current use for indicating the position of substituents in derivatives of acridine; these are shown in (I a) and (I b). The latter is still widely used, especially in Germany, but the former (I a) will be employed here.
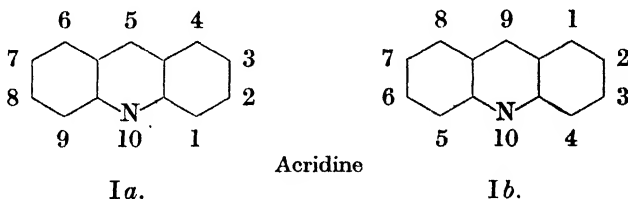
I a. Acridine I b.

For phenanthridine there are also two systems, (II a) and (II b), of which the former is used here.

Phenanthridine

II a. II b.
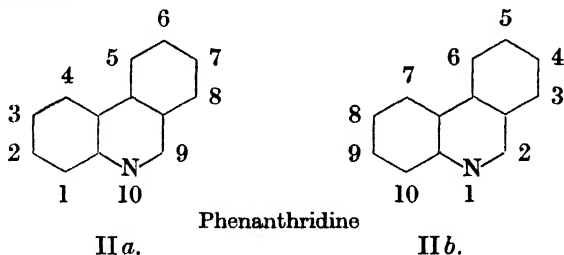
Acridine

Acridine is a solid, melting-point 110°, and occurs in the anthracene fraction of coal-tar. It has a marked irritant action on the skin and mucous membrane, and this is the origin of the name acridine. It is the parent substance of the acridine dyes,[3] some of which have valuable therapeutic properties.

Acridine is formed when the vapour of benzylaniline is passed through a red-hot tube.

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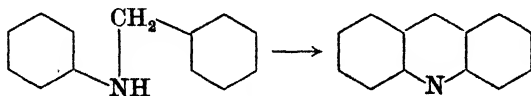
[1] A. Skita, Ber. 1924, 57, 1982.   [2] L. Helfer, Helv. Chim. Acta, 1926, 9, 814.

[3] For an account of these see Dye-stuffs derived from Pyridine, &c., by J. T. Hewitt, London 1922, p. 91 et seq.

Substituted acridines can be obtained by heating the acyl derivatives (including formyl) of diphenylamine with zinc chloride.
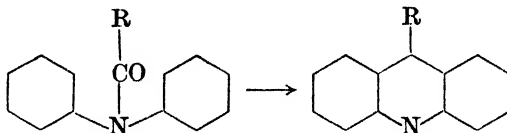
A reaction much used in the preparation of acridine dyes, many of which are amino derivatives, is the condensation of an aldehyde with a derivative of *m*-phenylene diamine. Heating with hydrochloric acid under pressure gives the dihydroacridine which is oxidized by ferric chloride to the salt of the true acridine. The following scheme shows the preparation of acridine yellow.
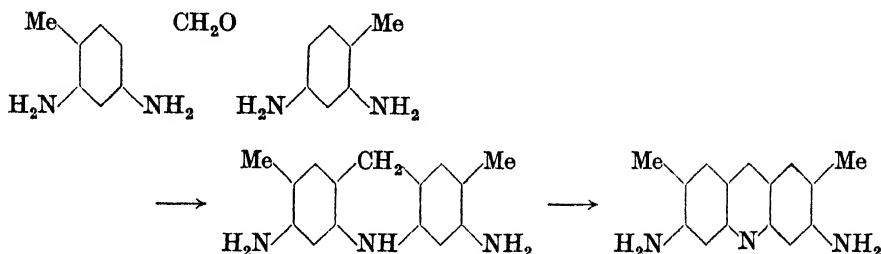
This compound behaves as a monoacidic base and its salts are dyes; there is the same possibility of resonance in the kation between structures in which each of the rings is benzenoid and quinonoid in turn and each of the nitrogen atoms carries the positive charge, as we have already discussed in dealing with the triphenylmethane and cyanine dyes. The following are some of the structures which must contribute to the resonance-hybrid.
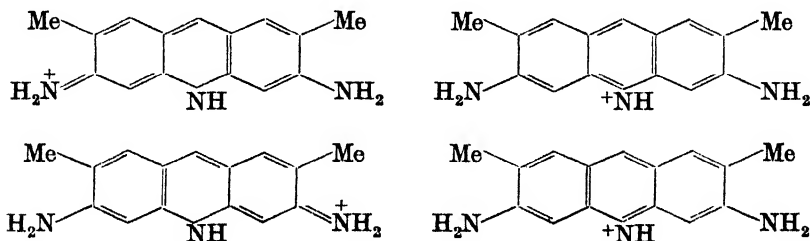
An important acridine derivative of this type is acriflavine or trypaflavine which is the methochloride of 2,8-diamino-acridine. It is prepared from 2,4,2'4'-tetranitro-diphenylmethane by reduction to the tetra-amino compound, followed by ring closure, oxidation, and formation of the methochloride.
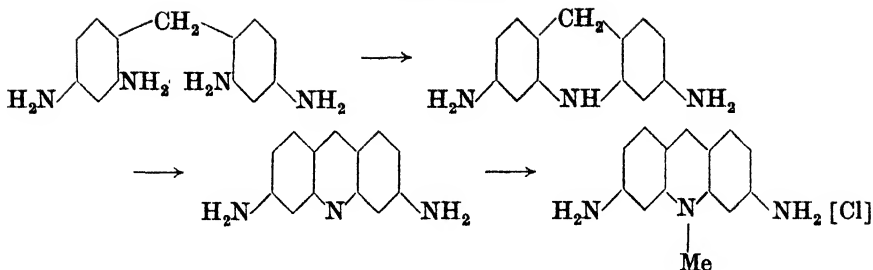
It has been used for the treatment of diseases caused by trypanosomes, such as the sleeping-sickness prevalent in certain parts of Africa, but its chief application is as a dressing for wounds because of its very powerful antiseptic properties. Proflavine has similar antiseptic properties; it is the sulphate of the diamino-acridine of which acriflavine is the methochloride.

Acridine is a very stable compound, and exhibits very feeble basic properties. It combines with alkyl halides to give the acridinium salts, which on oxidation with alkaline potassium ferricyanide yield the N-alkyl-acridones through the intermediate pseudo-base.
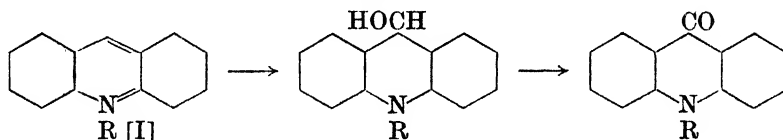
Acridine is easily reduced to 5,10-dihydroacridine, for example, with zinc dust and hydrochloric acid, and the dihydro compound is very readily oxidized to acridine, even by ammoniacal silver nitrate. Oxidation of acridine with potassium permanganate yields quinoline $\alpha\beta$-dicarboxylic acid, while oxidation of the acridinium compounds leads to derivatives of o-carboxydiphenylamine, $\phi \cdot NH \cdot C_6H_4 \cdot CO_2H$. When boiled with sodium bisulphite solution it yields 5,10-dihydroacridine-5-sulphonic acid.

Acridone, or 5-keto-5,10-dihydroacridine (III), may be prepared by oxidation of acridine with calcium hypochlorite in presence of cobalt salts, or by ring closure of phenylanthranilic acid with sulphuric acid at 100°.
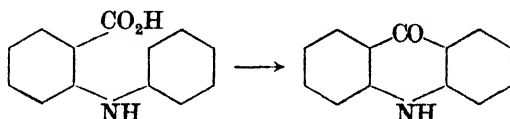
III.

It is an extremely stable substance, melting-point 354°, and it can even be distilled at ordinary pressure. Its structure is analogous to that of the γ-quinolones and raises many of the difficulties already discussed (p. 551). The evidence available is insufficient to decide the true constitution of the

compound. A very important acridine derivative is the valuable anti-malarial drug atebrin, the physiological action of which is similar to that of quinine. It is 2-chloro-5-(δ-diethylamino-α-methylbutyl)amino-7-methoxyacridine.

$$NH \cdot CHMe \cdot (CH_2)_3 \cdot NEt_2$$
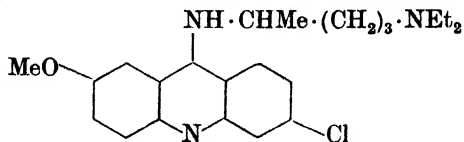
Phenanthridine

Phenanthridine (VI), melting-point 104°, boiling-point above 360°, may be prepared by passing the vapour of benzylidene-aniline (V) through a porcelain tube at 800°,[1] or by similar treatment of N-methylcarbazole (VII), a reaction similar to those by which pyridine and quinoline may be prepared from N-methyl-pyrrole and N-methyl-indole, respectively (p. 549).

V.   VI.   VII.
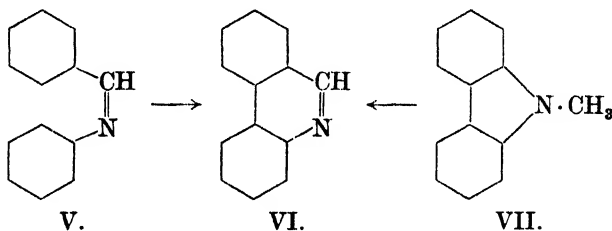
It is formed when the alkaloid tazettine is distilled with zinc dust.[2] A reaction of wider application for obtaining phenanthridines is the dehydration of the acyl derivatives of o-amino-diphenyl.

R·CO·NH   R·C═N
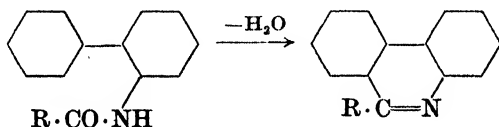
The dehydration was originally carried out by fusion with zinc chloride,[3] but a more satisfactory method is by heating for a short time with phosphorus oxychloride.[4] This method of dehydration, which recalls the Bischler-Napieralski synthesis of isoquinolines (p. 566), does not succeed in the case of the formyl derivatives.

Phenanthridone (9-keto-9,10-dihydrophenanthridine) may be prepared by the oxidation of phenanthridine by means of calcium hypochlorite and

[1] See G. Pyl, *Ber.* 1927, **60**, 287.
[2] E. Späth and L. Kahovec, ibid. 1934, **67**, 1501.
[3] A. Pictet and A. Hubert, ibid. 1896, **29**, 1182.
[4] G. T. Morgan and L. P. Walls, *J.C.S.* 1931, 2447; 1932, 2225.

cobalt nitrate.[1] Substituted phenanthridones can be obtained by the action of alkali hypobromite upon diphenamic acids,[2]

$$HO_2C \cdot C_6H_4 \cdot C_6H_4 \cdot CO \cdot NH_2;$$
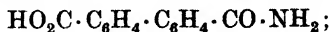
by the action of zinc chloride upon o-diphenylurethanes,[3]

$$C_6H_5 \cdot C_6H_4 \cdot NH \cdot CO_2Et;$$
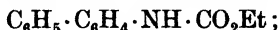
and by the action of phosphorus pentachloride or zinc chloride on fluorenone oxime;[4] the last reaction is an example of a Beckmann transformation which leads to the enlargement of a ring (compare p. 472).
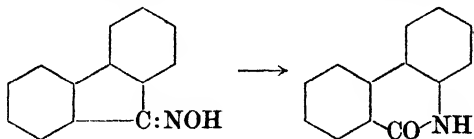
Phenanthridone is reduced to phenanthridine by heating with zinc dust; reduction of phenanthridine with tin and hydrochloric acid gives 9,10-dihydrophenanthridine. Phenanthridone when treated with phosphorus pentachloride gives 9-chlorophenanthridine. Addition of alkyl halides to phenanthridine gives the N-alkylphenanthridinium salts, which are converted by alkali into a mixture of the N-alkylphenanthridones, and N-alkyl-9,10-dihydrophenanthridines; these are formed by mutual oxidation and reduction of the pseudo-base.[5]

[1] A. Pictet and E. Patry, *Ber.* 1893, **26**, 1964.

[2] L. Oyster and H. Adkins, *J. Amer. C. S.* 1921, **43**, 208; F. J. Moore and E. H. Huntress, ibid. 1927, **49**, 1324.

[3] A. Pictet and A. Hubert, loc. cit.

[4] F. J. Moore and E. H. Huntress, *J. Amer. C. S.* 1927, **49**, 2618.

[5] A. Pictet and E. Patry, *Ber.* 1902, **35**, 2534.

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P p

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